Mechanical Debridement with Antibiotics in the Treatment of Chronic Periodontitis: *Effect on Systemic Biomarkers* A Systematic review

by

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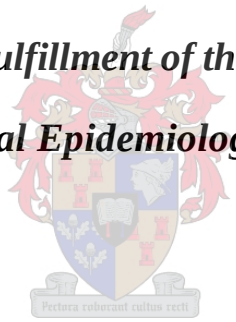

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ABSTRACT

BACKGROUND

Chronic periodontitis is an inflammatory oral disease which leads to the destruction of the supporting tissues of the teeth, leading to bone resorption and tooth loss. Destruction of the periodontal attachment apparatus can result in gingival recession and root furcation exposure in advanced stages resulting in tooth mobility and tooth loss. Mechanical debridement is the most frequent treatment for chronic periodontitis, in severe cases systemic antibiotics in conjunction with mechanical debridement have been used. The efficacy and the beneficial effect of this combination on the inflammatory biomarkers require further investigation.

OBJECTIVES

The aim of this systematic review was to assess the effectiveness of adjunctive antibiotics in the improvement of inflammatory systemic biomarkers in the treatment chronic periodontitis.

SEARCH METHODS

We searched the following electronic databases: Cochrane Oral Health Group Trials Register (30th June 2018). The Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library 2018 – current issue), MEDLINE (1966 to present), EMBASE (1982 to present), CINAHL via EBSCO (1990 -present), Google scholar (1990 - present). Web of Knowledge (1990 to May 2018), The meta-Register of Controlled Trials (www.controlled-trials.com), The US National Institutes of Health On-going Trials Register (www.clinicaltrials.gov). The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch) was searched to identify relevant trials for inclusion in the review. Conference proceedings, on-going trials registers (02/06/2018) and reference list of included articles were assessed for relevant trials. No language or date of publication restrictions applied.

SELECTION CRITERIA

We searched for randomised controlled trials (RCTs that evaluated the effectiveness of adjunct antibiotic therapy on the systemic biomarkers in the treatment of chronic periodontitis. All trials that compared adjunctive systemic antibiotics with mechanical debridement or

mechanical debridement alone, or scaling and root planning, oral hygiene and prophylaxis or placebo were included in the study.

DATA COLLECTION AND ANALYSIS

Two reviewers independently examined the titles and abstracts retrieved by the search to identify relevant trials for inclusion in the review. All included trials were assessed for risk of bias and data were extracted for further analysis. The primary outcomes assessed include:changes in serum/blood levels of inflammatory biomarkers such as Matrix Metalloproteinases (MMPs), Tissue Inhibitors of MMPs(TIMs), Cytokines, C-Reactive Protein(CRP) and Glycated haemoglobin(HbA1c). Secondary outcomes include periodontal indices such as bleeding on probing (BOP), gingival index (GI), clinical attachment level (CAL), plaque index (PI) and probing pocket depth (PPD).

MAIN RESULTS

Fourteen trials (n=1457 participants) were included in the review. Seven trials reported on MMP-8, with average of 3 months time to event. Five trials reported on IL-1β, three trials on IL-6 and two on IL-8 serum level. Four trials reported on CRP; while eight reported on HbA1c level and one on TIMP-1 level. Trials were assessed for risk of bias and judged as low, high, or unclear of risk of bias.

Six studies showed no significant differences in MMP-8 concentration level between the two intervention groups. Significant decrease (60%) in odds of increased MMP-8 levels during 2-year study was reported in one trial (OR 0.40, 95%CI: 0.21 to 0.77, p=0.006). One study reported no significant difference for TIMP-1 (0.96, 95% CI: 0.78 to 1.18, p=0.7), while two studies showed significant reduction in HbA1c (10%) at 3 months. Other studies reported no difference in HbA1c levels (%): (Mean (SD) 7.00 (0.76) versus 7.11 (0.99); p=0.710), (Median (Interquartile Range [IQR]) 6.3 (5.5,7.3) versus 6.7 (6.3, 7.7); p=0.8), (p=0.35, 0.55, 0.33, and 0.62, at baseline, 3 months, 6 months, and after 1 year of treatment respectively. Meta-analysis showed a mean reduction of 0.24mm in the periodontal pockets (PD) at 3 months [MD, -0.25 with 95% CI -0.38 to -0.12]. Two trials revealed no significant difference PD≤3mm at 3 months, [MD, -1, 95% CI -22.54 to 20.53 (p=0.19)]. A decrease in periodontal pockets(PD≥4mm) and a reduction of 3.38mm in favour of SRP+antibiotics after 3 months [MD, -3.38, 95% CI -6.51 to -0.25 (p=0.93, I^2=0%)] was observed for probing depth(PD). No significant difference in clinical attachment level (CAL) at 3 months [MD, -0.13, 95% CI -0.34 to 0.07; Chi^2=0.98, df=3, p=0.81, I^2=0%]. The overall quality of evidence was low largely

because of attrition bias (24%; 32%) connoting high risk of bias and wide confidence intervals which suggests imprecision of results.

AUTHORS' CONCLUSIONS:

There is limited but low-level of evidence suggesting that systemic antibiotic therapy combined with mechanical debridement improves the systemic biomarker levels during the treatment of chronic periodontitis.

Samevatting

Agtergrond

Chroniese periodontitis is ‘n inflammatoriese mondsiekte wat lei tot die vernietiging van die ondersteunende weefsel van die tande, en uiteindelik tot beenresorpsie en tandverlies. Vernietiging van die periodontale hegtingsorgane kan lei tot tandvleis-terugsakking en wortelaftakking-ontbloting en, in meer gevorderde stadiums, potensieel tot tandmobiliteits- en tandverlies. Tandsteenverwydering en wortelbeplanning, ook bekend as meganiese brokstukverwydering, is die behandeling wat die meeste op chroniese periodontitis toegepas word. Vir ernstige gevalle van periodontale siektes, is sistemiese antibiotika tesame met skalering en wortelbeplanning gebruik; die doeltreffendheid hierdie kombinasie benodig verdere ondersoek oor die voordelige uitwerking op die vlak van inflammatoriese biomerkers.

Doelwitte

Die doel van hierdie sistematiese oorsig was om die effektiwiteit van adjunktiewe (bykomende) antibiotika in die verbetering van inflammatoriese sistemiese biomerkers in die behandeling van chroniese periodontitis te assesseer.

Soekmetodes

Ons het deur die volgende elektroniese databasisse gesoek: Cochrane Oral Health Group Trials Register (30 Junie 2018), The Cochrane Central Register of Controlled Trials (Trials (CENTRAL) (Cochrane Library 2018 – jongste uitgawe), MEDLINE (1966 tot hede), EMBASE (1982 tot hede), CINAHL via EBSCO (1990 – hede), Google scholar (1990 – hede). Web of Knowledge (1990 tot Mei 2018), The meta-Register of Controlled Trials (www.controlled-trials.com), The US National Institutes of Health On-going Trials Register (www.clinicaltrials.gov). The World Health Organization International Clinical Trials Registry

platform (www.who.int/trialsearch) is ondersoek om relevante proefnemings vir insluiting in die oorsig te identifiseer. Relevante konferensieprosedures, deurlopende proefnemingsregisters (02/06/2018) en verwysingslyste van ingeslote artikels is vir relevante proefnemings geassesseer. Geen beperkings is geplaas op die taal of datum van publikasie toe die elektroniese databasisse ondersoek is nie.

Seleksiekriteria

Ons het gesoek na lukraak gekontroleerde proefnemings (RCT's) wat die effektiwiteit van adjunkte antibiotiese terapie op die sistemiese biomerkers in die behandeling van chroniese periodontitis geëvalueer het. Alle geïdentifiseerde RCT's wat adjunktiewe sistemiese antibiotika met meganiese verwydering alleen of met skalering en wortelbeplanning, mondhigiëne en profilakse of plasebo vergelyk, is in die studie ingesluit.

Dataversameling en -analise

Twee ondersoekende outeurs het onafhanklik van mekaar die titels en abstrakte bestudeer wat deur die soektog opgespoor is om die ingeslote proefnemings te selekteer. Elke ingeslote soektog is geassesseer vir risiko van vooroordeel (Sien risiko van vooroordeel-tabel) en relevante data is vir verdere analise onttrek. Ons primêr geassesseerde uitkomste is: veranderings in serum/bloedvlakke van inflammatoriese biomerkers soos (Matrix Metalloproteinases) MMPs, (Tissue Inhibitors of MMPs) TIMs, Cytokines, C-Reactive Protein(CRP) en Glycated haemoglobin (HbA1c). Sekondêre uitkomste sluit in periodontale aanduiders soos bloeding by ondersoek (BOP), tandvleis-indeks (GI), kliniese aanhegtingsvlak (CAL), plaak-indeks (PI) en diepte van ondersoek (PPD).

Belangrikste resultate

Veertien proefnemings (n=1457) is in die ondersoek ingesluit. Alle proefnemings het antibiotika versus plasebo gekombineer met meganiese verwydering vergelyk. Sewe proefnemings het MMP-8 gerapporteer, met 'n gemiddelde van 3 maande tot ryd van uitslag. Vyf proefnemings op IL-β, drie proefnemings op IL-6 en twee op IL-8 serumvlak. Daar is vier proefnemings op CRP gerapporteer; agt op HbA1c vlak en een op TIMP-1 vlak. Proefnemings is geassesseer vir risiko van partydigheid en geoordeel as synde laag, hoog, of onduidelik weens risiko van strydigheid. Ses studies het geen noemenswaardige verskille in MMP-8 konsentrasievlak tussen twee intervensiegroepe aangetoon nie. 'n Aansienlike afname (60%) in verskille van verhoogde MMP-8 vlakke gedurende 'n 2-jaarstudie is in een ondersoek (OR 0.40, 95%CI: 0.21 tot0.77, p=0.006) gerapporteer. Een studie het gewys op

een nie-opvallende verskil vir TIMP-1 (0.96, 95% CI: 0.78 tot 1.18, p=0.7). Slegs twee studies het aansienlike verlaging in HbA1c (10% verlaging op 3 maande) aangetoon, terwyl ander geen opvallende verskil in HbA1c-vlakke aangetoon het nie (%): (Gemiddelde (SD) 7.00 (0.76) versus 7.11 (0.99); p=0.710), (Mediaan (Interkwartiel-omvang [IQR]) 6.3 (5.5,7.3) versus 6.7 (6.3 7.7); p=0.8), (p=0.35, 0.55, 0.33, en 0.62, op 3 maande, 6 maande, en ná 1 jaar van behandeling onderskeidelik. ‘n Studie het na 3 maande (1.5%) versus (0.9%) aangetoon; geen aansienlike verskil op 3 maande nie (p=0.22). Meta-analise vertoon ‘n gemiddelde verlaging van 0.24mm in die periodontale sakke (PD) op 3 maande [MD, -0.25 met 95% CI -0.38 tot -0.12], terwyl twee proefnemings geen beduidende verskil PD≤3mm op 3 maande, [MD, -1 met 95% CI -22.54 tot 20.53 (p=0.19)] aangetoon het nie. ‘n Afname in periodontale sakke (PD≥4mm) en ‘n verlaging van 3.38mm ten gunste van die SRP + antibiotika na 3 maande [MD, -3.38 met 95% CI -6.51 tot -0.25 (p=0.93; I^2=0%)])] is vir ondersoekdiepte (PD) waargeneem. Geen aansienlike verskil in kliniese hegtingsvlak (CAL) op 3 maande [MD, -0.13 op 95% CI -0.34 tot 0.07; Chi^2=0.98, df=3, p=0.81, I^2=0%]. Gehalte van bewys is geassesseer deur GRADEpro en het lae voorkoms van effektiwiteit van adjunkte sistemiese antibiotika in die behandeling van chroniese periodontitis aangetoon.

Skrywers se gevolgtrekkings

Daar is beperkte maar laevlak-bewyse wat suggereer dat sistemiese antibiotiese terapie gekombineer met meganiese verbrokkeling die sistemiese biomerkervlakke gedurende die behandeling van chroniese periodontitis verbeter.

ABBREVIATIONS

CRP: C-reactive protein; CVD: cardiovascular disease; DM2: diabetes mellitus type2

GCF: gingival crevicular fluid; HbA1c: glycosylated haemoglobin; IL-1β: interleukin-1-beta; IL-6: interleukin-6; IL-8: interleukin-8; MMP-8: matrix metallo-proteinase-8; NCD: non-communicable disease; NSPT: non-surgical periodontal disease; PMNs: polymorphonuclear neutrophils; RCT: randomised controlled trial; SES: socioeconomic status; SRP: scaling and root-planing; TIMP-1: tissue inhibitor metallo-proteinase-1; TNF-α: tumour necrosis factor alpha.

BACKGROUND

DESCRIPTION OF THE CONDITION

Periodontal disease is one of the most common public health concerns worldwide (Tonetti 2017). It is a chronic inflammatory disease of the periodontium and the most prevalent infectious oral condition (Nazir 2017). Although periodontal disease is treatable and can be prevented, it is the most frequent cause of tooth loss in adults with about 5 - 15% prevalence in most populations (Petersen 2003). The signs and symptoms of periodontitis includes: persistent halitosis, red or swollen gingiva, tender/ bleeding gingiva, painful mastication, loose teeth and gingival recession. Worldwide, the prevalence of the disease varies in different countries, in the United States of America (USA), about 50% of the adult population above 30 years of age present with some form of periodontitis, ranging from mild to severe periodontitis (Eke 2015). According to Kassebaum (2010), severe chronic periodontitis (SCP) was rated the 6th most prevalent non-communicable disease (NCD) in the world, affecting 10.8% of the population (Uncertainty Interval 10.1% - 11.6%); translating to 743 million people across the Globe (Kassebaum 2014). Additionally, prevalence of SCP increases with age, revealing a steep increase between the 3rd and 4th decades of life, with a spike in incidence around the age of 38. At the age of 40, the prevalence of SCP reaches its peak (Kassebaum 2014).

The etiology of periodontitis is complex and includes the presence of specific pathogens, such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia* in a susceptible host (Trinidade 2008). Recent systematic reviews and prospective studies identified certain potential risk factors which increases the odds of periodontitis. Among these are tobacco use (Lorenzo 2015), diabetes (Löe 1993), unhealthy diet (Adegboye 2012), genetic factors (Liu 2012), stress (Laforgia 2015) and excessive alcohol consumption (Adegboye 2012). Central to the disease process of periodontitis is the formation of biofilm on tooth and root surfaces of the tooth which triggers the immune system. The inflammatory host response affects the tissues surrounding the teeth, resulting in destruction of the periodontal apparatus (Novak 2002). In its advanced stage, periodontitis can lead to difficulty in mastication and speech and can adversely affect general well-being and quality of life (Johansson 2006). The diagnosis of periodontal disease is based on clinical measures of inflammation, such as bleeding on probing, pocket probing depth and attachment loss, as well as radiological evidence of bone destruction (Bolerazska 2016).

Above all, the effects of periodontitis appear to manifest beyond the local oral tissues, affecting the systemic environment (Needleman 2004; O'dowd 2010). Several studies have suggested an association between certain NCDs, socioeconomic status (SES), adverse pregnancy outcome and periodontal infection (Gomes-Fihlo 2010; Lalla 2011; Tonetti 2013). Furthermore, periodontitis has been associated with certain conditions, such as cardiovascular disease (Blaizot 2009), diabetes (Hu 2004; Wang 2007; Dehghan 2007; Pradhan 2001), respiratory disease (Scannapieco 2003) and systemic inflammatory conditions (Nadeem 2009; Lamster 2016).

Periodontal treatment entails the elimination of biofilm and microbial deposits from the root surfaces in order to reduce the inflammatory host response and tissue destruction (Kepic 1990; Hinrichs 1985). Although there are several treatment approaches for periodontitis, conservative mechanical debridement (scaling and root planing [SRP]) has been the most common therapy (Matthews 2014). Depending on the severity of inflammation, mechanical debridement combined with systemic antibiotic use has been advocated as a treatment option. However, there is currently insufficient scientific evidence to support or refute whether systemic antibiotics effectively enhances the results of mechanical periodontal treatment (Monte-bugnoli 2005; Iwamoto 2003; Heitz-Mayfield 2009; Tüter 2007; Emingil 2011; O'Connell 2008).

The most studied inflammatory biomarkers in relation to periodontitis include:

1. Matrix Metalloproteinases (MMPs)

2. Tissue Inhibitors of MMPs (TIMPS)

3. Cytokines/Interleukins (IL-1β, IL-6 & IL-8)

4. C-Reactive Protein (CRP)

5. Glycosylated Hemoglobin (HbA1c)

TNF-α is a cytokine, which has been omitted from the review, as it exhibits an early rise and fall after an inflammatory stimulus, being an unstable biomarker, with very low basal levels that escape most commercial detection assays (D'Aiuto 2013).

Matrix Metalloproteinases (MMPs)

MMPs are a group of proteolytic enzymes that play an important role in the degradation of collagen and extracellular matrix in conditions such as osteoarthritis, tumour cell invasion, rheumatoid arthritis and autoimmune skin lesions (Birkedal-Hansen 1993). In the periodontal disease process, fibroblasts, neutrophils, macrophages, keratinocytes and endothelial cells can produce MMPs. MMP-8 is a significant biomarker in periodontitis and also known as collagenase-2 or neutrophil collagenase.

Tissue Inhibitors of MMPs (TIMPs)

TIMPs are endogenous tissue regulators of MMP activity. A variety of cells produce TIMPs, including endothelial cells, fibroblasts, macrophages and keratinocytes (Birkedal-Hansen 1993). In periodontitis, the TIMPs and MMPs proportion is disturbed/skewed toward higher levels of MMPs (Preshaw 2004). TIMPs have an inhibitory effect on MMP-8 and MMP-9, enzymes which predominantly destroys type-1 collagen in periodontitis.

Cytokines

Cytokines are a group of proteins released in response to an activating stimulus and they function through binding to specific cellular receptors (Lagdive 2013), being produced by a variety of cells in the human body (Birkedal-Hansen1993). Interleukins are among the cytokines that seem to be linked to the inflammatory response seen in chronic periodontitis (Takashiba 2003).

Interleukin-1β (IL-1β)

IL-1β is responsible for bone resorption and has an inhibitory effect on bone formation. It stimulates prostaglandin synthesis and facilitates the up-regulation of inflammatory response (Faizuddin 2003).

Persons with periodontitis have increased IL-1β levels, which can be measured in the GCF as well as in the periodontal tissues. The IL-1β functions as a biomarker for periodontal destruction. Studies have found a correlation between levels of IL-1β and the severity of periodontitis (Masada 1990).

Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine, which regulates the host response to tissue injury, inducing formation of CRP (Dasanayake 2009). Together with IL-1, IL-6 facilitates tissue destruction by elevating the MMP levels (Okada 1998).

IL-6 is produced by monocytes, vascular endothelial cells, osteoblasts and fibroblasts in reaction to inflammatory challenges (Haba 2011). They promote immunoglobulin production by plasma cells and are co-stimulators of T-cell activation (Scully 2003). In periodontitis, initial host response is part of the acute-phase response initiated by the activation of fibroblasts, endothelial cells and local macrophages, which lead to the release of the TNF-α, IL-6 and IL-1β mediators (Qvarnstrom 2010).

Interleukin-8 (IL-8)

IL-8 is a constituent of the IL-8 supergene family, that is capable of activating polymorphonuclear leukocytes (PMNs) which is the reason why it has also been linked to inflammation (Chung 1997). Lagdive (2013) has found that high levels of IL-8 in the GCF of adult patients correlated with destruction of the periodontal tissues.

C-Reactive Protein (CRP)

CRP is produced by the liver and considered as a biomarker for several conditions, such as inflammatory disorders, osteomyelitis, systemic inflammation, neoplasms, vasculitis and rheumatoid arthritis (Paraskevas 2008). High sensitivity CRP (hsCRP) can estimate cardiac and transient ischaemic attack (TIA) (Paraskevas 2008). Several studies support the finding of high levels of serum CRP in patients with periodontitis (Paraskevas 2008). Danisia Haba (2011) proposed that the higher levels of CRP in chronic periodontitis patients could make them more susceptible to cardiovascular disease.

Glycated Haemoglobin (HbA1c)

Diabetes Mellitus is one of the most studied risks factors for periodontal disease. Studies have reported that poor glycaemic control is correlated with higher risk for periodontal disease (Mealey 2006). It has been suggested that there is a 2-way relationship between glycaemic control and periodontal disease (Tervonen 1997). Improvement in glycaemic control seems to decrease the risk for periodontitis while periodontal treatment might improve

glycaemic levels in type 2 diabetes mellitus patients (Sanchez-Zamora 2014). Glycaemic control is rated as one of the most important factors in the prevention of diabetes complications. Glycated haemoglobin (HbA1c) is used as an indicator of serum glucose levels during the 4-month life-cycle of the red blood cell, thus being a surrogate marker for glycaemic control (Higgins 2013).

Periodontitis treatment regimens

Periodontal therapy without antibiotics

There are numerous studies illustrating the positive effects of Scaling and Root planning (SRP) alone on systemic biomarkers (Fiorini 2013; Ghodpage 2014; Moeintaghavi 2012; Sexton 2011). Good glycaemic control seems to be a pre-requisite for mechanical debridement to have a decreasing effect on HbA1c in periodontitis patients with type 2 diabetes mellitus (Kaur 2015; Dag 2009; Raman 2014; Wei 2011). Several randomised clinical trials (RCT) have suggested the efficacy of mechanical debridement in decreasing HbA1c levels in blood (Moeintaghavi 2012; Kiran 2005; Zhang 2013; Chen 2012; Koromantzos 2012; Li 2011; Faria-Almeida 2006; Artese 2015; Engebretson 2013; Madden 2008). Regarding MMP-8 levels, a study showed that salivary MMP-8 decreases after mechanical debridement (Sexton 2011). A number of studies reported on IL-1β level, the efficacy of SRP was documented in the following studies: Sexton 2011 confirmed reduction in salivary IL-1β levels; blood/circulating IL-1β levels (Al-Mubarak 2002; Ide 2003) and decreased in GCF IL-1β levels (Fiorini 2013). The GCF levels of TIMP-1 have also shown a decrease after mechanical debridement (Ghodpage 2014).

Amongst the RCT's evaluating IL-6 levels, four studies revealed a decrease in circulating/blood IL-6 levels (Artese 2015; Vidal 2009; Tonetti 2007) and GCF IL-6 levels (Fiorini 2013) after mechanical debridement. With regards to IL-8, three studies demonstrated a decrease in salivary IL-8 levels (Sexton 2011), GCF IL-8 levels (Fiorini 2013) and circulating IL-8 levels (Artese 2015). Ten RCTs demonstrated a decrease in blood CRP levels after mechanical debridement/SRP alone (Raman 2014; Chen 2012; Koromantzos 2012; Vidal 2009; Tonetti 2007; Koppolu 2013; Kamil 2011; Bokhari 2012; Michalowicz 2009; Taylor 2010).

Periodontal therapy with antibiotics

Currently, evidence suggests that mechanical debridement together with doxycycline antibiotics [or sub-antimicrobial-dose doxycycline (SDD)] decreases the HbA1c levels in blood biomarkers in type 2 diabetes mellitus (O'Connell 2008; Promsudthi 2005; Tsalikis 2014; Gaikwad 2013; Gilowski 2012; Botero 2013; Jones 2007; Singh 2008; Rodrigues 2003; Yun 2007; Engebretson 2007).

Concerning TIMP-1, SDD was able to down-regulate gingival crevicular fluid (GCF) levels of EMMPRIN, which is an up-regulator of MMP's, and this was associated with increased TIMP-1 levels (Emingil 2008). Other reports also suggest that doxycycline associated with non-surgical periodontal treatment (NSPT) increased GCF TIMP-1 levels (Gorska 2006; Choi 2004). Lower IL-6 levels have been reported in both GCF (Emingil 2011; Choi 2004) and serum (O'Connell 2008; D'Aiuto 2005) after NSPT and antibiotic therapy. GCF MMP-8 levels have also shown a reduction in many studies on SRP combined with antibiotics (Tsalikis 2014; Gilowski 2012; Choi 2004; Lee 2004; Tüter 2010; Emingil 2004).

Reduced serum CRP and IL-1β levels have also been associated with NSPT combined with SDD (D'Aiuto 2005; Koppikar 2013; Lopez 2012; Giannopoulou 2016; Almaghlouth 2014). Lastly, salivary IL-8 levels decreased after SRP and antibiotic therapy (Guentsch 2008).

Antibiotics used in the treatment of periodontitis

A wide variety of systemic antibiotics have been used in the treatment of periodontitis. The most widely used are: Amoxicillin (AM), Azithromycin (AZ), Clarithomycin (CLAR), Doxycycline (DOX), Metronidazole (MET), Moxifloxacin (MOX), Ornidazole (ORN) and Clavulanate (CLAV). AM combined with MET is the most popular combination in the treatment of periodontitis (Garcia Canas 2015).

Reasons for excluding Aggressive Periodontitis from this review

Chronic periodontitis is characterized by periodontal tissue destruction which is commensurate with local factors, with progression ranging from slow to moderate. However, in aggressive periodontitis, there is rapid progression of attachment loss in systemically healthy patients. The scale of tissue destruction is disproportionate to the amount of plaque

and calculus (Sadeghi 2018). Other reasons for excluding aggressive periodontitis from this review include:

(i) Genetics

Studies have shown that very few subgingival bacterial species differed between chronic and aggressive periodontitis patients (Heller 2012), which has led to studies on genetic predisposition (Kinane 2001) and familial patterns of disease (Baer 1971; Meng 2011; Rapp 2010) as potential risk factors for aggressive periodontitis.

(ii) Local Risk Factors

In aggressive periodontitis, there is a lack of relationship between local etiologic factors and the amount of periodontal destruction (Baer 1971). In contrast, in chronic periodontitis, local factors play a major role (Albandar 2002).

(iii) Rate of Bone Loss

In aggressive periodontitis, the rate of bone loss has been described as 3-4 times higher than the rate of progression of chronic periodontitis (Baer 1971; Schatzle 2003).

Lastly, aggressive periodontitis and chronic periodontitis share common disease manifestations and outcomes since they are likely to represent two distinct disease categories with differences with regards to disease progression, underlying causes and risk factors.

(iv) Hyper-responsive phenotype

Aggressive periodontitis requires systemic diseases to be excluded for its diagnosis (Moharamzadeh 2018) to be established. Since our study population consisted of patients with co-morbidity, Trials that on aggressive periodontitis were excluded.
In aggressive periodontitis, the macrophage phenotype is hyper-responsive, together with elevated prostaglandin (PG)E_2, and Interleukin (IL)-1β in response to bacterial endotoxins (Lu 1994). The hyper-responsive in aggressive periodontitis would likely cause a spike in the IL-1β levels, which could lead to very high base-line levels of IL-1β which could confound the treatment effects thereby producing a bias in the study. Thus, trials on aggressive periodontitis were excluded from the study.

(v) Actinobacillus Actinomycetemcomitans (AA)

The levels of Actinobacillus Actinomycetemcomitans (AA) are significantly elevated in aggressive periodontitis patients (Asikainen 1991). Our treatment modalities consisted primarily of non-surgical periodontal therapy (NSPT) with antibiotics as an adjunct. In the case of aggressive periodontitis, NSPT and surgical periodontal therapy are not sufficient for the elimination of AA in localized aggressive periodontitis (Moharamzadeh 2018). AA invades the soft tissues and produces leucotoxins, immunosuppressive factors and collagenase (MMPs) (Könönen 2014). Here again, we anticipated conducting a meta-analysis on the MMP-8 biomarker subgroup. However, due to the elevated AA's in aggressive periodontitis which would not subside even in spite of NSPT, this would lead to elevated baseline levels of MMP-8 in the aggressive periodontitis patients and once pooled with MMP-8 from chronic periodontitis patients, we would not be able to ascertain the true effect of antibiotics combined with SRP on aggressive nor chronic periodontitis patients.

Studies evaluating local antibiotics

Studies assessing the effects of local antibiotics on periodontitis will not be included the review. Several reviews on local antibiotics in the form of antimicrobial irrigants (Magnusson 1998; Nagarakanti 2015; Gjermo 1993), chlorhexidine chips (Cosyn 2006) and subgingival chlorhexidine gel (Cosyn 2005) has shown less effective results. Magnusson (1998) reported little long-term efficacy of antimicrobial irrigants, while Cosyn (2006) reported limited and conflicting results. Nagarakanti (2015) stated that evidence was insufficient regarding potential benefits of subgingival irrigation. Gjermo (1993) reported that subgingival antibacterial agents have no effects on periodontitis. In their review (Cosyn 2005), it was concluded that subgingival chlorhexidine gel administration was not a justified treatment. In contrast, a review (Jepsen 2000) showed additional pocket depth reduction and attachment gain associated with local antimicrobials. Hussein (2007) also reported improved clinical outcomes with the use of locally delivered antibiotics. Since most of the studies have not been able to confirm the efficacy of local antimicrobials in the treatment of periodontitis, their application has been excluded from the current review. Moreover, Mombelli (2012) has stated that amoxicillin and metronidazole when systemically administered is a superior form of treatment and no other regime has shown superiority in the treatment of periodontal disease.

DESCRIPTION OF THE INTERVENTION

Previous meta-analyses (Herrera 2002; Drisko 1996; Winkelhoff 1996) and systematic reviews (Elter 1997; Moreno Villagrana 2012; Hayes 1992) have looked at the benefits of antimicrobial agents in providing systemic clinical benefit. Another study suggested that systemic antibiotic therapy is effective in reaching micro-organisms, which are otherwise inaccessible to scaling instruments and local antibiotic therapy (Bidault 2007). SRP alone (without adjunctive antibiotics) has been shown to reduce the risk for cardiovascular disease (CVD) and diabetes mellitus by improving plasma levels of inflammatory (CRP, IL-6, TNF-α) and metabolic (HbA1c) markers of endothelial function (Teeuw 2014).

HOW THE INTERVENTION MIGHT WORK

Several molecules have been identified as potential biomarkers for periodontal disease, including proteins, cytokines, receptors and enzymes. These biomarkers have been identified and measured in the gingival crevicular fluid (GCF), which provide information on the local periodontal destruction, in serum and saliva. In saliva, high levels of matrix metallo-proteinases (MMPs, including MMP-8, MMP-14 and TIMP-1) have been associated with periodontitis (Sorsa 2004). Marcaccini (2010) reported that salivary MMP-8 and MMP-9 can be used as indicators of periodontal treatment response. Systemically, serum or blood biomarkers have been associated with periodontal disease. The level of C-reactive protein (hs-CRP) and inflammatory cytokines in serum have been linked to periodontitis (Nakajima 2010). Periodontitis leads to the production of local inflammatory mediators, which have the potential to enter the systemic circulation, thus causing an inflammatory burden (Susanto 2012). An increase in the serum C-reactive protein (CRP) levels is indicative of the inflammatory burden, as seen in periodontitis patients (Noack 2001; Craig 2003; D'Aiuto 2004; Salzberg 2006; Linden 2008; Pitiphat 2008). Simultaneously, bacteria and their products can enter the systemic circulation causing an infectious burden (Susanto 2012). Circulating oral bacteria stimulate hepatocytes to secrete CRP (Mealey 2006; Li 2000; Soell 2007). Increased levels of CRP associated with periodontitis result in insulin resistance and subsequent impaired control of blood glucose in type 2 diabetes mellitus (DM2) (Hu 2004; Wang 2007; Dehghan 2007; Pradhan 2001), which in turn increases the levels of HbA1c (Taylor 1999; Nesse 2009).

WHY IT IS IMPORTANT TO DO THIS REVIEW

Mechanical debridement combined with proper oral hygiene measures can reduce or prevent further periodontal damage in individuals with periodontitis. Several studies have suggested that combining antibiotics with mechanical debridement and oral hygiene (SRP) could reduce periodontal disease drastically. The effects of antibiotic combined with mechanical debridement on blood biomarkers, however, needs to be established. Diabetes mellitus and cardiovascular diseases are among the systemic diseases that have huge economic burden worldwide. Periodontal treatment has been shown to reduce glycemia and lower HbA1c levels in diabetic patients (Dag 2009; Botero 2013; Jones 2007; Wang 2014; Javed 2014). Meta-analyses also support a positive effect of periodontal treatment on glycemic control (Li 2015; Liew 2013).

The potential economic benefit of periodontal therapy on glycemic control can have a significant impact in terms of health care costs. Brod (2016) pointed out that the annual costs per person for missed work-time due to post-prandial hyperglycemia (PPH) was considerable and estimated it at €394.78 in Germany (given €8.48 per week; 40 work weeks), £396.83 in the UK (given £8.62 per week; 46 work weeks) and U$606.30 in the USA (given U$13.05 per week; 47 work weeks).

With regards to cardiovascular diseases (CVD), periodontal therapy has been shown to reduce the risk for CVD by improving plasma levels of inflammatory, thrombotic and metabolic markers (Tüter 2007; Teeuw 2014; Koppolu 2013; Bokhari 2012) and changing the systolic blood pressure (D'Aiuto 2006). In addition, periodontal therapy normalized haematological markers levels in CVD sufferers (Taylor 2010) and reduced low grade systemic inflammatory markers and lipid profile (Caúla 2014). Researchers have reported that the direct costs of CVD were a cumulative U$272 Billion for the USA (Laslett 2012), with an annual estimate of €106 Billion for the European Union (Eur Heart Network). A plethora of studies has declared the benefits of periodontal therapy on the reduction of CRP levels, which is directly related to cardiovascular health. These findings, if proven to be conclusive, can translate into a substantial reduction in the economic burden of diabetes and CVD**.**

OBJECTIVES

To conduct a systematic review of the effectiveness of systemic antibiotics as an adjunctive therapy to mechanical treatment in the improvement of inflammatory systemic biomarkers as compared to mechanical debridement alone in chronic periodontitis. The study will be a systematic review and not a RCT.

METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

TYPES OF STUDIES

All randomised controlled trials (RCTs) where the use of systemic antibiotics combined with mechanical debridement versus mechanical debridement alone or with placebo were included.

TYPES OF PARTICIPANTS

Studies with participants diagnosed with chronic periodontal disease were included. Studies with participants having co-morbidity such as diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease or chronic kidney disease (minimum 18 years and above), and chronic periodontitis were also included.

Apoptosis is a process which involves morphological and biochemical events in the cell resulting in its death and its elimination by phagocytes (Cohen 1991). Neutrophils from individuals with both diabetes and chronic periodontitis displayed a significant decrease in apoptosis as compared to people with diabetes or chronic periodontitis alone. Caspases are cytosolic proteases which bring about the apoptotic morphology in a cell and their presence is a hallmark of apoptosis activation (Gammonal 2001). The caspase-3 activities were also reduced drastically in these systemically compromised individuals as compared to healthy individuals with chronic periodontitis (Hasturk & Kantarci 2015). Increased caspase activation has been detected in inflamed gingival biopsies while no caspase activation was observed in healthy tissue (Bantel 2005). This finding implies that periodontitis-associated tissue damage involves caspase activation. An example on the therapeutic value of antibiotics is that of azithromycin which reduces the expression of Toll-like receptors (TLR),

TLR-2 (Karlström 2011) and TLR-4 (Maezono 2011, Iwamoto 2011), thereby promoting the recruitment of neutrophils which TLR-2 and TLR-4 seek to inhibit.

Azithromycin improves the phagocytosis of apoptotic neutrophils (Hodge 2006). Once the polymorphonuclear leukocytes (PMNs) are infiltrated by azithromycin, the release of azithromycin is very slow. This sustained retention of azithromycin by PMNs facilitates delivery and release of the drug at the site of infection (Hand 2001). Azithromycin also reduces PMN chemotaxis and induces PMN apoptosis.

Severe inflammation resulting in local tissue destruction occurs when neutrophil apoptosis is inhibited (Stockley 2006). Decreased levels of IL-1β, IL-8, TNF-α and MMP-8 have also been observed following azithromycin administration in chronic and aggressive periodontitis (Ho 2010, Lai 2011, Han 2012, Emingil 2012). It therefore clear that there is a difference in the host response to antibiotics in a healthy individual compared to an individual with a co-morbidity during periodontal treatment. Therefore the results from this review should be interpreted with caution.

The immune responses in different individuals has been noted and has been discussed above. Currently, the association between chronic periodontitis (CP) and non-communicable disease (NCDs) is a relatively recent development and of global interest (Global Burden of disease), thus, we have flagged the need to interpret the results with caution as immune responses between healthy individuals and sick individuals could vary substantially.

TYPES OF INTERVENTIONS

All interventions that included mechanical debridement combined with adjunctive systemic antibiotics for the treatment of chronic periodontitis were considered for inclusion.

Chronic periodontitis is defined as an infectious oral disease leading to an inflammatory response within the supporting tissues of the teeth, resulting in progressive attachment and alveolar bone loss (Flemming 1999). The clinical features include- colour, texture and volume alterations of marginal gingivae, periodontal pocket formation, bleeding on probing (BOP), bone loss, furcation exposure and drifting and exfoliation of teeth (Moharamzadeh 2018). ACAL/PD>4 mm with or without BOP in chronic periodontitis (Mdala 2014) while periodontal pockets equal to or greater than 6 mm in advanced stages (WHO 2005).

Prior to 2018, The American Academy of Periodontology (AAP) classified periodontal disease into into 8 main groups: - Gingival diseases, 3 types of periodontitis (chronic, aggressive and manifestation of systemic diseases),and four additional periodontal conditions which include: necrotizing periodontal diseases, abscesses in the periodontium, periodontitis associated with endodontic lesions and acquired or developmental deformities and conditions (Armitage 1999). A new classification based on stage and risk of disease progression was proposed in March 2018. The new classification includes a sound medical and dental history taking and detailed clinical assessment to identify cases of periodontal disease. The steps and procedure for periodontal disease diagnosis includes:

- Medical history and risk factors, e.g. diabetes, smoking, hypertension, medications, substance abuse, HIV/AIDS, pregnancy, or other existing conditions that may affect treatments
- Dental history including the chief complaint(s)
- Extra-oral examination
- Intra-oral examination
- Teeth examination including occlusal aspects and pulpal status
- Radiographic examination
- Periodontal examination, including presence and distribution of plaque and calculus, assessment of periodontal and peri-implant soft tissues, and measurement of probing depth, gingival recession (or enlargement) and bleeding on probing at six sites per tooth. Furcation lesions and mucogingival aspects should be carefully explored (FDI).

Other important indicators such as genetic conditions, microbiologicaland host biomarkers could also aid clinical diagnosis (Armitage 2013).

New Classification of Periodontitis

Very recently, the 2017 World Workshop Classification System for periodontal and peri-implant diseases was developed (Dietrich 2018).
In the 2017 classification system, the demarcation between chronic and aggressive periodontitis was removed due to there being insufficient evidence from biological studies that

chronic and aggressive periodontitis were separate conditions. They were seen to be merely variations of the same disease process.

Necrotising Periodontitis and Periodontitis as a manifestation of systemic disease are the only other forms of periodontitis recognized by the 2017 classification system (Papapanou 2018).

Upon being diagnosed as having periodontitis, Staging and Grading are performed as per the criterion set-out by the 2017 classification system.

The basic classification of the 2017 World Workshop on Periodontal Diseases are as follows in 3 broad sections, namely:

Periodontal health, gingival diseases and conditions:

Periodontal health (comprising of either: intact periodontium OR, reduced periodontium)

Gingivitis: dental biofilm-induced (comprising of either: of intact periodontium OR, reduced periodontium)

Gingival diseases and conditions: non-dental biofilm-induced

Periodontitis (comprising of either: Necrotising periodontal diseases OR, Periodontitis OR, Periodontitis as a manifestation of systemic disease).

Other conditions affecting the periodontium (comprising of either Systemic diseases or conditions affecting the periodontal supporting tissues, OR, Periodontal abscess and endodontic-periodontal lesions, OR Mucogingival deformities and conditions, OR, Traumatic occlusal forces, OR, Tooth and prosthesis and related factors).

TYPES OF OUTCOME MEASURES

PRIMARY OUTCOMES

- Changes in serum/blood levels of inflammatory biomarkers such as:

1. MMPs
2. TIMPs
3. Cytokines
4. CRP

5. Glycated haemoglobin (HbA1c)

SECONDARY OUTCOMES

- Gingival index
- Plaque index
- Pocket depth and
- gingival recession

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

To identify studies for this review, we adopted the following search terms and strategy: "anti-bacterial agents" [medical subject headings {MeSH}] OR "anti-infective" OR "systemic antibiotics" OR "antibiotic OR "antibiotic therapy") AND (periodontitis OR "chronic periodontitis" OR "periodontal diseases" [MeSH] OR "periodontitis" [MeSH]. The search terms and strategies were used to identify relevant trials in MEDLINE database. The same method was appropriately used for each of the other relevant databases searched.

Electronic database search was combined with hand search to identify trials for inclusion in the review. Attempts were also made to identify unpublished and grey literature. RCTs published from 1980 to May 2018 were considered for inclusion. **See appendix 1** for used search terms.

ELECTRONIC SEARCHES

The following databases were searched for relevant trials:

Cochrane Oral Health Group's Trials Register

CENTRAL – Cochrane Register of Controlled Trials (of the Cochrane Library – current issue)

MEDLINE (1966 to present)

EMBASE (1982 to present)

CINAHL (1990 -present)

Google scholar (1990 - present)

ONGOING TRIALS DATABASES

We searched the following on-going trials registers (02/06/2018) to identify relevant trials using the term 'periodontal disease' and 'systemic antibiotics' OR antimicrobial OR 'mechanical debridement'.

The metaRegister of Controlled Trials (www.controlled-trials.com) The US National Institutes of Health On-going Trials Register (www.clinicaltrials.gov). The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch)

SEARCHING OTHER RESOURCES

Reference lists and Correspondence: We searched reference lists of all included studies and reviewed articles for relevant trials. (21/09/2018)

We also contacted authors of included studies and experts in the field of oral health care to identify any additional published or unpublished trials. (16/08/2018).

We also searched the ProQuest database, Stellenbosch University database and Google scholar (10/08/2018). See Appendix 1 for search terms.

HAND SEARCHING

Trials published prior to 1991 were hand searched since no indexing terms for randomized trials in MEDLINE existed (Lefebvre 2009). All trials in parts of journals (supplements and conference abstracts) which were not routinely indexed in databases such as MEDLINE were hand searched. We did not apply any date or language restrictions.

DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

Two review authors, Sudhir Munasur (SM) and Eunice Turawa (ET) independently screened the titles and abstracts of the search output to identify and select potentially eligible studies [Figure1]. Applying eligibility criteria using a pre-designed eligibility form based on the inclusion criteria, duplicate studies and studies that were not relevant to the review were excluded. Full-text articles of potentially relevant studies were retrieved, and disagreements

were resolved through discussion or, if required, a third author would add his input to enable a consensus on such review (Usuf Chikte (UMEC)). The reference lists for the included studies were screened for additional studies.

DATA EXTRACTION AND MANAGEMENT

Data extraction form was designed for extraction of relevant information. For eligible studies, two review authors (SM and ET) extracted the data using the data extraction form. The following data were extracted from each study:

- Authors, trial-year, country of study, funding, whether university based or not.

- Specific trial characteristics: the type of study population, age, gender, periodontal disease diagnosis and severity, number of participants recruited and number of participants completing the trial, withdrawals and the reasons thereof, overall sample size.

- Primary and secondary outcomes. In case of missing data, the authors of the reports were contacted. For each outcome, we extracted the arithmetic mean and standard deviation (or information to estimate the standard deviation). We resolved discrepancies through discussion or, if required, we consulted the third author (UMEC). We checked for accuracy and when information regarding any of the above is unclear, we contacted authors of the original reports to provide further details.

STUDY QUALITY ASSESSMENT

Two review authors (SM and ET) independently and in duplicate performed a quality assessment of the included studies. All trials that met the inclusion criteria were assessed on four major criteria: randomization method, concealment of allocation, blinding of patients and care providers, and accurate description of withdrawals and drop outs.

Any disagreements between the review authors were resolved by consensus. Quality, criteria, the definition thereof was based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Risk of bias for each study was assessed independently by the 2 review authors (SM and ET) using the criteria outlined in The Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). The method used for allocation sequence generation, the completeness of the outcome report, selective reporting and any other source of bias that can put a study at high risk of bias were assessed (**Appendix 2**). Any disagreements were resolved by discussion or by consulting a 3rd assessor.

MEASURES OF TREATMENT EFFECT

Mean Difference (MD), with its corresponding 95% confidence interval (CI), was used as the effect size for continuous data that were measured using the same scale (for instance, pocket depth (mm)). There were no cases where continuous data were measured using different scales of measurement, in which case the Standardized Mean Difference (SMD) would have been used. For binary data, use of the risk ratio (RR) was anticipated with its corresponding 95%CIs; however, included studies did not report the necessary raw data to calculate these and in most cases odds ratios (OR) were reported or p-values according to the study authors. In other instances, the significance of the differences between the treatment-arms was reported according to the study authors as there were no relevant data to calculate treatment effects.

UNIT OF ANALYSIS ISSUES

Cluster randomized trials were not included in this systematic review and therefore there was no need to adjust analyses for clustering. There were four studies where there were more than two treatment arms, however, there were no meta-analysis data that needed choosing two treatment arms for analysis to avoid double counting the participants from the same control arm.

DEALING WITH MISSING DATA

Study authors were contacted to recover missing data on either outcomes or risk of bias though we did not receive any responses. Levels of attrition were noted in the included studies and assessed under risk of bias section. For each outcome in each trial, the

denominator was calculated using the number of randomized subjects minus any participants whose outcomes were missing.

ASSESSMENT OF HETEROGENEITY

Heterogeneity was assessed using the Chi-squared-based Q-statistic method (using $p<0.1$ to indicate statistical significance due to the low statistical power of this particular test) and the I^2 measurement (where values 50% or higher indicated significant heterogeneity).

ASSESSMENT OF REPORTING BIASES

We had intended to assess the likelihood of publication bias by assessing the asymmetry of funnel plots, however, this could not be done due to insufficient number of studies in our meta-analyses.

DATA SYNTHESIS

We performed random effects meta-analysis using RevMan 5.3 software for some continuous secondary outcomes. Results were reported as mean differences with appropriate 95% CI and displayed using forest plots. Due to insufficient data, many outcomes could not be meta-analysed, and we took the narrative approach in reporting the results.

SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

We had intended to identify potential sources of heterogeneity through subgroup analysis with respect to the following patient characteristics (self-reported smoking status, initial pocket probing depth, immunological disease (HIV), patient adhered plaque control) or treatment characteristics (class of antibiotics, baseline and follow-up time, number of sessions for debridement, supportive follow-up care). Due to insufficient data we could not perform these subgroup analyses

SENSITIVITY ANALYSIS

Also due to insufficient data, no sensitivity analyses were performed.

RESULTS

DESCRIPTION OF STUDIES

RESULTS OF THE SEARCH

After de-duplication of identified relevant trials in the EndNote reference, electronic search yielded 602 references. These 602 title and abstracts were screened independently and in duplicate by two review authors (ET and SM), and 58 records were retained for further assessment. The full-text articles of these 58 trials were retrieved and screened for eligibility. A total of 42 trials were excluded with reasons (See table of characteristics of excluded studies). We finally included 16 trials in this review (Almaghlouth 2013; Botero 2013; Engebretson 2011; Gaikwad 2010; Gilowski 2012; Golub-Lee 2008; Grossi 1997; Han 2012; Jones 2007; Lopez 2011; Miranda 2014; O'Connell 2008; Payne 2011; Reinhardt 2010; Saleh 2016 and Tüter 2007), (See figure 1 and table of characteristics of included studies). We reported on 14 trial results considering that three results (Golub-Lee 2008; Payne-Golub 2011; Reinhardt 2010) were from the same trial but reported differently by the authors, we therefore reported the three trials as one. Figure1 shows the study selection process.

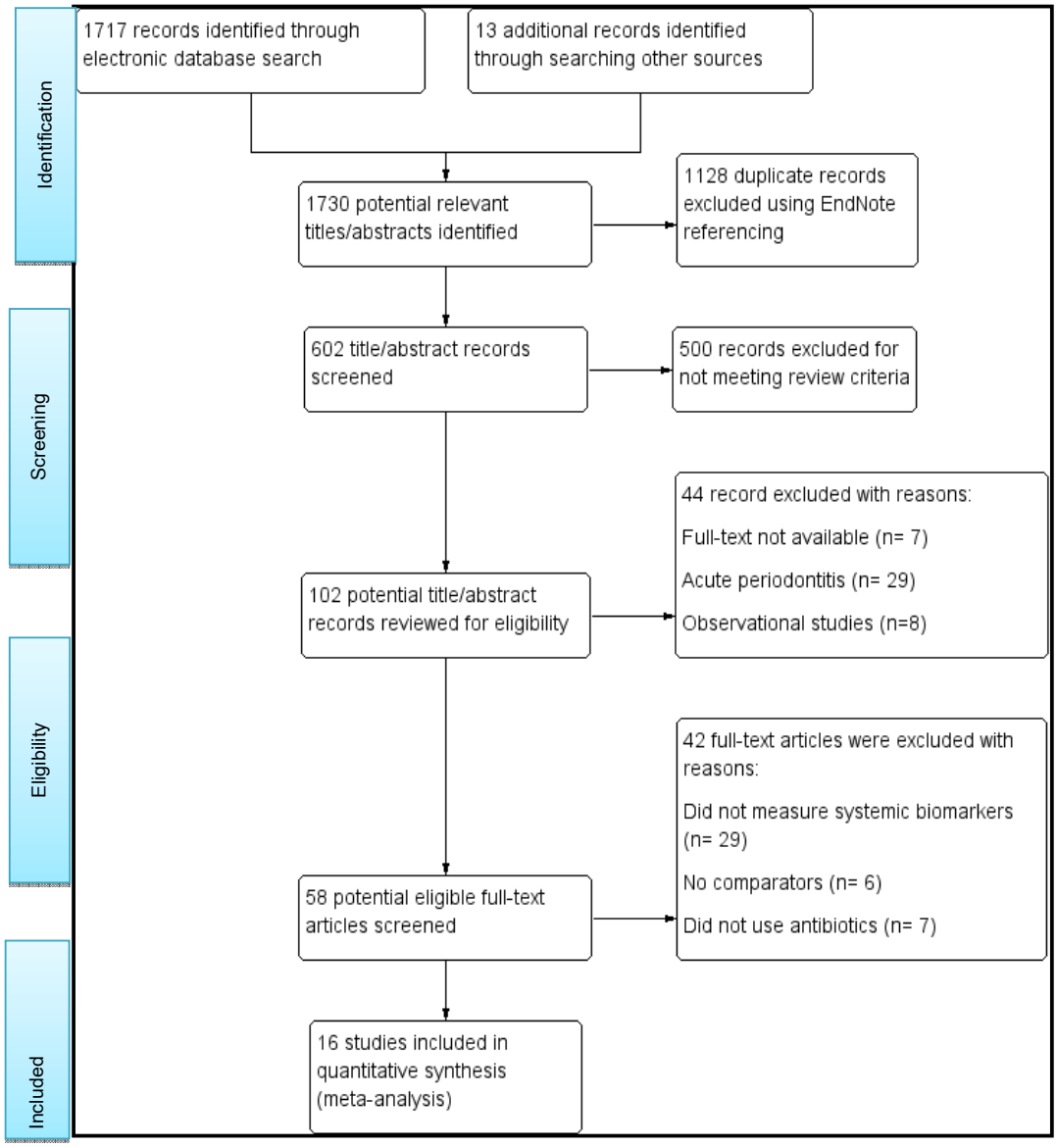


FIGURE 1: FLOW DIAGRAM OF STUDY SEARCH

INCLUDED STUDIES

A total of 16 randomised controlled trials were identified and assessed for inclusion in this review (Almaghlouth 2013; Botero 2013; Engebretson 2011; Gaikwad 2010; Gilowski 2012; Golub, Lee 2008; Grossi 1997; Han 2012; Jones 2007; Lopez 2011; Miranda 2014; O'Connell 2008; Payne 2011; Reinhardt 2010; Saleh 2016 and Tüter 2007). Three reports originated from the same trial (Golub,Lee 2008;Payne 2011 and Reinhardt 2010). All included trials assessed and compared the effect of antibiotics versus placebo or no antibiotic, with mechanical debridement in either arm.

STUDY SETTING

Five of the included trials were conducted in developed countries. Three trials were conducted in the USA: Engebretson 2011, Grossi 1997, and Jones 2007. The trial by Saleh 2016 was conducted in Australia, while Almaghlouth 2013 was conducted in Switzerland. Two trials Han 2012 and Tüter 2007 were conducted in Turkey; while trials by Miranda 2014 and O'Connell 2008 were conducted in Brazil. The trial by Lopez 2011 was from Chile, and the trial by Botero 2013 was conducted in Coloumbia. Trials by Gaikwad 2010 and Gilowski 2012 were conducted in India and Poland respectively. All trials were conducted in an academic hospital, one study was a multicentre study (Jones 2007) while others were conducted in a single centre.

CHARACTERISTICS OF THE PARTICIPANTS

In total, 1457 participants (14 trials) were included in the analysis for this review. Participants were all diagnosed with moderate-to-advanced chronic periodontitis. The age of the participants spanned between 18-70 years old. Seven trials (Botero 2013; Engebretson 2011; Gaikwad 2010; Gilowski 2012; Grossi 1997; Jones 2007 and O'Connell 2008) included participants with hyperglycaemia (Diabetes); one trial (Tuter 2007) recruited participants with coronary artery disease (CAD), while Lopez 2011 included participants with metabolic syndrome (MetS). Three trials (Almaghlouth 2013; Han 2012; and Saleh 2016) included adults with chronic periodontal disease and Golub-Lee 2008 comprised of participants with osteopenic menopausal women (See characteristics of included table).

CHARACTERISTICS OF INTERVENTIONS AND COMPARISONS

All included trials assessed the effect of antibiotics compared with placebo or no antibiotic with mechanical debridement in either arms (See Table of characteristics of included studies). The intervention groups had broad spectrum antibiotics as an adjunct to the non-surgical therapies received. Combination of interventions varied across included trials (See Table 4 for details).

Two trials (Botero 2013 and Han 2010) evaluated the effect of Azithromycin 500mg in the treatment group compared to placebo in the control group. About 53% of the trials (Engebretson 2011; Gaikwad 2010; Jones 2007; Gilowski 2012; Golub-Lee 2008; Grossi 1997; O'Connell 2008 and Tüter 2007) examined the effects of doxycycline in the test group (TG), while the control group (CG) received varied therapy ranging from no treatment to placebo.

Lopez 2011, Miranda 2014 and Almaghlouth 2013 assessed the effect of Metronidazole 250mg, 400mg and 500mg respectively along with Amoxicillin 500mg, except for Almaghlouth 2013 which was Amoxicillin 375mg. Lopez 2011 and Miranda 2014 used placebo for the control group while the control group in Almaghlouth 2013 had Chlorhexidine mouth-rinse. Saleh 2016 is a three-arm trial, the first group received Metronidzole 200mg with Amoxicillin 500mg three times daily for 7 days while the second arm had scaling and root planing (SRP) followed by Azithromycin 500mg three times daily for 7 days. The last arm (Control group) received placebo for 7 days.

OUTCOMES

PRIMARY OUTCOMES

Almaghlouth (2013) reported on the following biomarkers: IL-1β, IL-6, IL-8, and CRP, while Gilowski 2012 recorded changes in MMP-8 and HbA1c level. Gaikwad 2013, Jones 2007, Botero 2013, Engebretson 2011, Grossi 1997 and Miranda 2014 measured the changes in HbA1c levels. Golub-Lee 2008 and Han 2012 reported on MMP-8 while Lopez 2011 estimated CRP serum level and Tüter 2007 quantified the levels of CRP and MMP-8.

O'Connell (2008) assessed and reported on IL-1β and HbA1c serum level. As mentioned earlier, the studies Golub-Lee 2008, Reinhardt 2010 and Payne,Golub2011 are based on the same experimental population and assignment arms (one trial). Golub-Lee 2008 gave a detailed report on the trial; hence it was our study under consideration; He measured IL-1β and MMP-8 while Reinhardt 2010 gave estimates on IL-1β and MMP-8. *Payne,*Golub *2011* reported on level of IL-1β, IL-6, CRP, MMP-8 and TIMP-1.

SECONDARY OUTCOMES

Almaghlouth (2013) reported on probing pocket depth/probing depth (PD) in mm. Engebretson (2011) estimated PD, clinical attachment loss (CAL) and percentage sites with plaque at baseline only. There was no data was found for 3 or 6 months post-baseline. Six trials, (Gaikwad 2010; Gilowski 2012; Grossi 1997; Lopez 2017; Miranda 2012; O'Connell 2008) measured CAL and PD. However, most of the results were portrayed in figures only and they could not be extracted accurately for further analysis.

Jones (2007) reported periodontal pocket depth (sites in percentage) but the data from baseline to 4 months was incomplete therefore the data could not be used. Han (2012) measured PD sites (percentage), however the data from baseline to 4 months was missing. Botero (2013) and Saleh (2016) measured pocket probing depth (PPD), CAL and plaque index (PI) while Tüter 2007 reported on PD, CAL and PI.

Golub-Lee (2008) did not measure any secondary outcomes while Reinhardt (2010) reported no baseline values for relative clinical attachment loss (rCAL), and (Payne,Golub 2011) did not report any secondary outcomes.

EXCLUDED STUDIES

After scrutinizing the full-text papers, 42 trials were excluded from further analysis with reasons. The trials did not meet the pre-specified criteria in the protocol. The reasons for exclusion are detailed in the Characteristics of excluded studies tables.

RISK OF BIAS IN INCLUDED STUDIES

Two authors independently assessed risk of bias in each of the included trials. The assessments were made in accordance with chapter 8 (pp 187 – 241): "Assessing risk of bias in included studies" of the *Cochrane Handbook for Systematic Reviews of Interventions, 1st Edition* (Higgins 2008). The judgments regarding the risk of bias in each of the included studies were reported in the "Characteristics of included studies". Summary tables of risk of bias in all trials are also displayed in **Figure 2 and Figure 3.**

One trial was judged to be at high risk of bias (Jones 2007). Four trials were judged to be at low risk of bias (Lopez 2007; Miranda 2011; Saleh 2016; Reinhardt 2010) while Eleven trials (Botero 2011; Engebretson 2011; Gaikwad 2010; Gilowski 2012; Golub-Lee 2008; Grossi 1997; O'Connell 2008; Payne,Golub 2011; Tüter 2007; Almaghlouth 2011; Han 2004) were judged as unclear of risk of bias. The available information from these trials was vague and insufficient to enable us to judge whether they are at "low risk or high risk of bias". The authors were contacted through series of emails for more information on the trials, but we did not receive response from them. Risk of bias table was completed for each of the included trials (Characteristics of included studies table; Figure 2 and Figure 3)

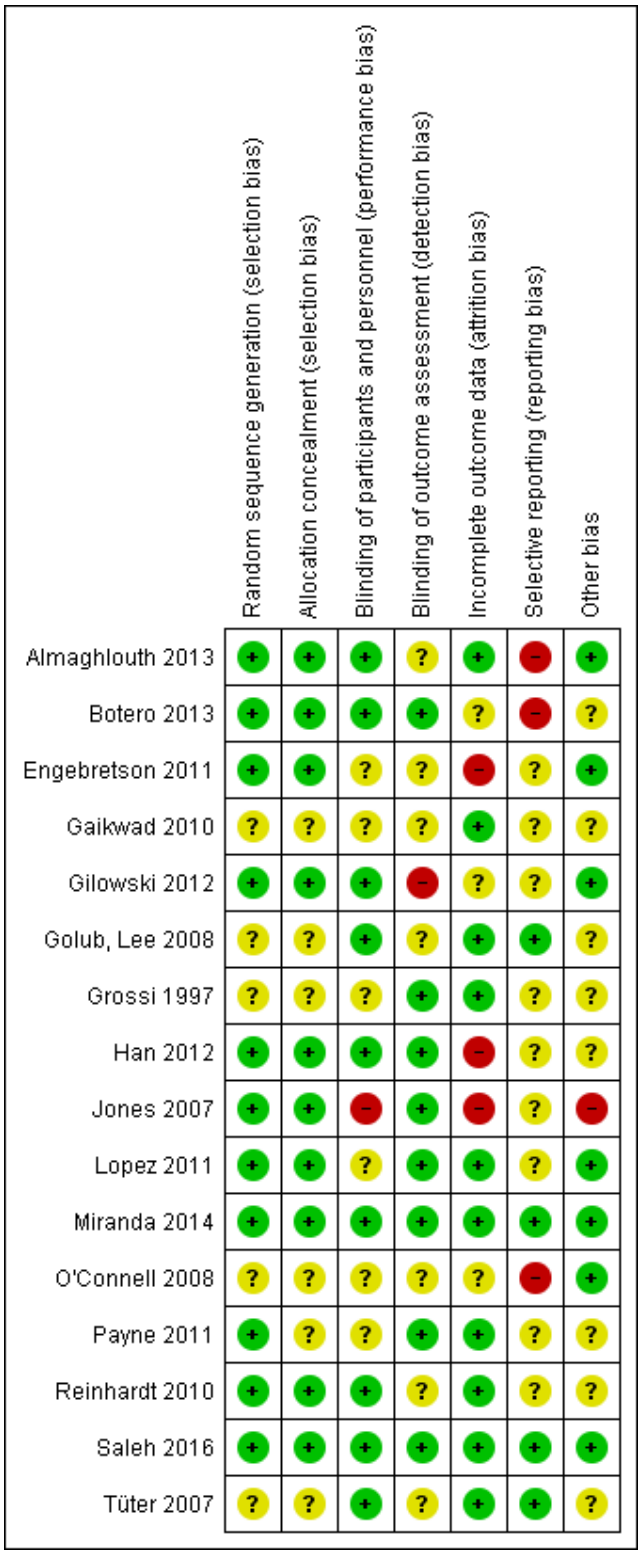


Figure 2: RISK OF BIAS SUMMARY

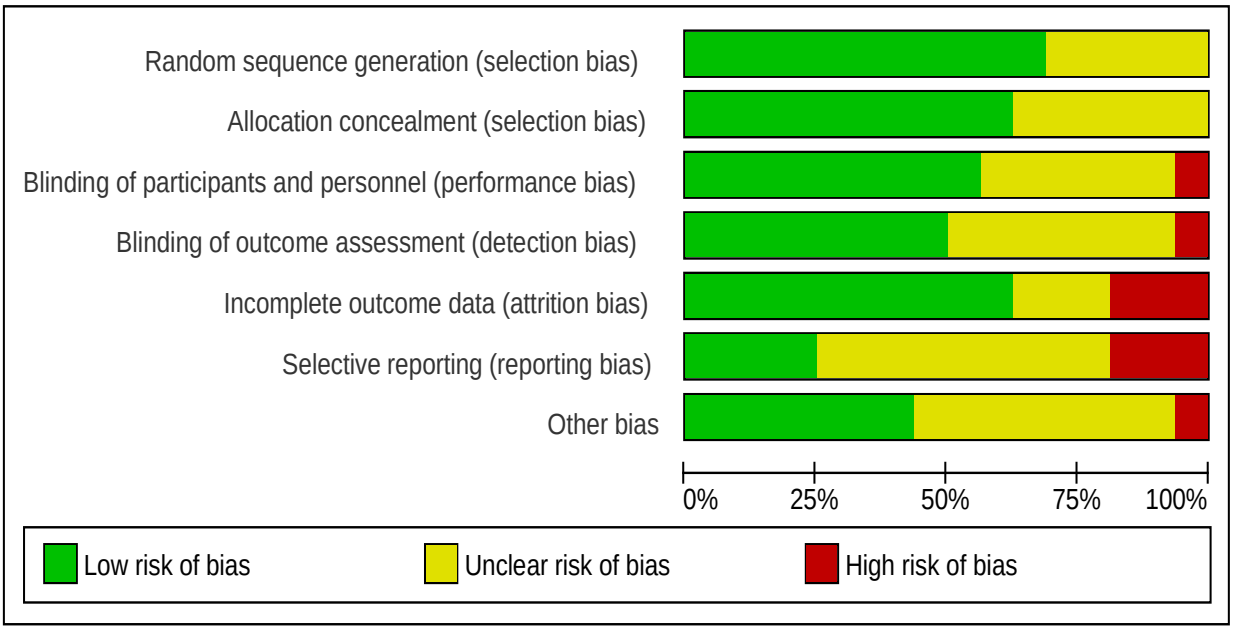


FIGURE 3: RISK OF BIAS GRAPH

ALLOCATION (SELECTION BIAS)

Trials were judged for selection bias based on adequate random sequence generation and allocation concealment. Eleven trials (Almaghlouth 2013; Botero 2013; Engebretson 2011; Gilowski 2012; Han 2012; Jones 2007; Lopez 2011; Miranda 2014; Payne 2011; Reinhardt 2010; Saleh 2016) reported adequate sequence generation, thus were judged as low risk of selection bias in terms of random sequence generation. Ten trials (Almaghlouth 2013; Botero 2013; Engebretson 2011; Gilowski 2012; Han 2012; Jones 2007; Lopez 2011; Miranda 2014; Reinhardt 2010; Saleh 2016) reported adequate allocation concealment and were judged as having low risk of selection bias in terms of allocation concealment. Five trials were judged to be at unclear risk of selection bias in terms of random sequence generation (Golub-Lee 2008; Grossi 1997; O'Connell 2008; Gaikwad 2010; Tüter 2007) on account of insufficient information on allocation concealment while six trials were judged to be at unclear risk of selection bias in terms of allocation concealment (Payne,Golub2011; Gaikwad 2010; Golub-Lee 2008; Grossi 1997; O'Connell 2008; Tüter 2007).

BLINDING (PERFORMANCE BIAS AND DETECTION BIAS)

Trials were judged for performance bias based on adequate blinding of participants, personnel and blinding of outcome assessors.

The study by Jones (2007) was judged to be at high risk of performance bias in terms of blinding of participants and personnel, because the participants, dentist, dental technician and assistant were not masked. Nine trials (Almaghlouth 2013; Botero 2013; Gilowski 2012; Golub-Lee 2008; Han 2012; Miranda 2014; Reinhardt 2010; Saleh 2016; Tüter 2017) were assessed to be at low risk of performance bias in terms of blinding of participants and personnel. Lopez (2011) was judged to be unclear of risk of performance bias, only the participants were masked. The dentist, dental assistant and dental technician were not masked. Five studies (Engebretson 2011; O'Connell 2008; Gaikwad 2010; Grossi 1997; Payne,Golub 2011) were judged to be at unclear risk of performance bias in terms of blinding of participants and personnel due to insufficient information. Several attempts to contact the authors of the trials for more information were unsuccessful.

Eight trials (Grossi 1997; Han 2012; Jones 2007; Lopez 2011; Miranda 2014; Payne,Golub 2011; Saleh 2016; Botero 2013) were judged to be at low risk of detection bias in terms of blinding of outcome assessment. Gilowski (2012) was judged to be at high risk since the statisticians and data committee saw the unblinded data. The remaining seven trials (Almaghlouth 2013; Engebretson 2011; Gaikwad 2010; Golub-Lee 2008; O'Connell 2008; Reinhardt 2010; Tüter 2007) were judged to be unclearof detection bias in terms of blinding of outcome assessment. They were also judged as "unclear" of risk of bias for the following reasons: Almaghlouth (2013) and Engebretson (2011) did not report whether the assessor was masked or not. Gaikwad (2010) did not report details on masking of the personnel. Golub-Lee (2008) did not report whether the assessor was masked or not. O'Connell (2008) did not mention if the operator was blinded or not. Reinhardt (2010) did not report on whether the assessor was masked or not. Tüter (2007) also did not report whether the assessor was masked or not.

INCOMPLETE OUTCOME DATA (ATTRITION BIAS)

Trials were assessed for attrition bias based on incomplete outcome data.

Eleven trials (Almaghlouth 2013; Botero 2013; Golub-Lee 2008; Grossi 1997; Lopez 2011; Miranda 2014; Payne,Golub 2011; Saleh 2016; Tüter 2007; Gaikwad 2010; Reinhardt 2010) were judged to be at low risk of attrition bias in terms of incomplete outcome data. Three trials (Han 2012; Jones 2007; Engebretson 2011) were judged to be at high risk of attrition bias for the following reasons: Han (2012) excluded 22% of the participants and reasons for exclusion were not provided. Jones (2007) had 32% of participants not completing the study, we were not sure whether the reasons forthe drop-out were related to adverse effects of the intervention or not. Engebretson (2011) had a 24% withdrawal and loss to follow-up. The reasons and the arm of intervention with the loss to follow up were not reported. Two trials (Gilowski 2012; O'Connell 2008) were judged to be unclear risk of attrition bias due to inadequate information on follow up. The authors were contacted through series of emails for the missing data, but there was no response from them.

SELECTIVE REPORTING (REPORTING BIAS)

Included trials were assessed for selective reporting. The following four trials (Golub-Lee 2008; Miranda 2014; Saleh 2016; Tüter 2007) were judged to be at low risk of selective reporting bias. Three trials (Almaghlouth 2013; Botero 2013; O'Connell 2008) were judged to be at high risk of selective reporting bias due to the following reasons: Almaghlouth (2013) did not make a distinction between patients receiving antibiotics or placebo. Botero (2013) did not report the value that was calculated between the two treatment groups. O'Connell (2008) did not provide separate data/results for the intervention group and placebo group. Nine trials (Engebretson 2011; Gaikwad 2010; Gilowski 2012; Grossi 1997; Han 2012; Jones 2007; Lopez 2011; Payne 2011; Reinhardt 2010) were judged to be at unclear risk of selective reporting bias due to the following reasons:

Engebretson (2011), presented incomplete data. Gaikwad (2010) did not provide the number of participants in each trial arm at 4 months. Four trials (Gilowski 2012; Grossi 1997; Jones 2007; Lopez 2011) gave a graphical representation which could not be interpreted accurately. Han (2012) reported the primary outcome while the secondary outcome reporton baseline to

4 months was missing. Payne, Golub (2001) gave an incomplete report. Reinhardt (2010) reported on the primary outcomes, but the secondary outcomes did not have baseline values.

OTHER POTENTIAL SOURCES OF BIAS

Jones (2007) had 5% difference at baseline between the “Usual” treatment group and “Early” treatment group for the Insulin only medications. Reinhardt (2010) did not report whether the telephone call was recorded by the call-centre for verification purposes.

EFFECTS OF INTERVENTIONS

A total of 14 trials were included in the review including three reports of the same study (Golub-Lee 2008; Payne,Golub 2011; Reinhardt 2010). The trials assessed the comparison of antibiotics versus placebo or no antibiotic with mechanical debridement in either of the arms.

TABLE 1: SUMMARY OF FINDINGS TABLES

Antibiotics versus no antibiotic/placebo for treatment of Chronic Periodontitis

Antibiotics versus no antibiotic/placebo for treatment of Chronic Periodontitis

Patient or population: Patients diagnosed with chronic periodontitis

Setting: Tertiary Hospital

Intervention: Systemic antibiotic

Comparison: Placebo

PERIOD	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Antibiotics versus no antibiotic/placebo					
PD (mm) at 3 months assessed with: Antibiotics versus no antibiotics/ usual care in the treatment of periodontal disease follow up: 6 months	**See comment**	The mean PD (mm) at 3 months in the intervention group was 0.25 fewer (0.38 fewer to 0.12 fewer)	-	276 (6 RCTs)	⊕⊕◯◯ LOW[a]	This information was not available
HbA1c assessed with: Antibiotics versus no antibiotics/ usual care in the treatment of periodontal disease in diabetes mellitus follow up: median 3 months	**Moderate**		-	600 (8 RCTs)	⊕⊕◯◯ LOW[a,b]	This information was not available
	See comment	See comment				
MMP_8	**Study population**		See	234	⊕⊕◯◯	Information notavailable

Antibiotics versus no antibiotic/placebo for treatment of Chronic Periodontitis

Patient or population: Patients diagnosed with chronic periodontitis

Setting: Tertiary Hospital

Intervention: Systemic antibiotic

Comparison: Placebo

PERIOD	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Antibiotics versus no antibiotic/placebo					
assessed with: Antibiotics versus no antibiotics/usual care in the treatment of periodontal disease in diabetes mellitus follow up: mean 6 months	See comment	See comment	comment	(4 RCTs)	LOW[a]	This information was not available
	Moderate					
	See comment	See comment				
CRP assessed with: Antibiotics versus No antibiotics follow up: mean 3 months	**Study population**		not estimable	354 (4 RCTs)	⊕⊕◯◯ LOW[a]	This information was not available
	See comment	See comment				
	Moderate					
	See comment	See comment				

Antibiotics versus no antibiotic/placebo for treatment of Chronic Periodontitis

Patient or population: Patients diagnosed with chronic periodontitis

Setting: Tertiary Hospital

Intervention: Systemic antibiotic

Comparison: Placebo

PERIOD	Anticipated absolute effects*(95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Antibiotics versus no antibiotic/placebo				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **MMP-8:** Matrix metalloproteinase-8; **CRP:** C-reactive protein

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by 1 because of unclear of risk of bias, and wide confidence intervals.

b. Downgraded by 1 because of unclear of attrition bias and reporting bias, and inadequate information on study methods.

PRIMARY OUTCOMES

1. IL-1β

Three trials reported on IL-1β (Almaghlouth2013; Golub-Lee,2008; O'Connell 2008). Almaghlouth (2013) assessed 40 participants (19 receiving antibiotic and remaining 21 placebo) and observed peak values of IL-1β in four patients at baseline (values ranging from 4.8 to 226.5 pg/ml), but no peak values were detected in any of the patients after 3 months. The patients in the test group received antibiotics for 7 days (three times per day). The peak serum amoxicillin concentration is normally reached in 1-1.5 hours post oral-administration with a terminal elimination half-life of 1.2 hours and 94% bioavailability (Mostafavi 2006). The peak serum metronidazole concentration is normally reached in 1-2 hours post oral-administration with a half-life of 6-8 hours and 100% bioavailability (Anderson 2012). Even though the effect of the antibiotics were present for a short duration of 7-8 days, but during the time there was a peak in concentration, there was an impact on the disease. The authors gave no indication on how many of the four received antibiotics. Golub-Lee (2008) assessed GCF IL-1β levels in 128 postmenopausal women (64 in SDD antibiotic group and 64 in placebo group) with chronic periodontitis,however there was no significant difference in the median GCF IL-1β levels between the two treatment groups after 1-year or 2-years timepoint. O'Connell 2008 evaluated 30 participants with type 2 diabetes patients and periodontitis (15 intervention and 15 placebo) but found no reduction in the concentration of IL-1β between baseline and 3 months (it remained at mean (SE) of 0.3(0.3) pg/ml); however, the trial authors did not give separate results for the intervention and placebo groups.

2. IL-6

Three trials reported IL-6 (Almaghlouth 2013; O'Connell 2008 and Payne-Golub 2011). Almaghlouth 2013 reported that a participant had a peak value of IL-6 of 216.3 pg/ml at baseline out of 40 periodontally diseased participants but there were no participants with peaked values after 3 months. Meanwhile, it is not clear whether the participants received antibiotic or placebo. O'Connell (2008) reported a decrease in IL-6 in the mean value (2.1;0.3(standard error (SE)) at baseline to 1.1 (0.2) at 3 months (p=0.005) for 30 participants with type 2 diabetes and periodontitis; however, the authors did not give separate values for the intervention group and control groups except to say “there were no significant differences observed between treatment groups”. Payne-Golub (2011) showed no significant difference in

IL-6 level between the antibiotic group (SDD) and placebo group in 128 post-menopausal women with chronic periodontitis after 2 years (40% SDD versus 46% placebo; OR 0.72, 95%CI: 0.30 to 1.69, p=0.4).

3. IL-8

Almaghlouth (2013) reported a peak value in IL-8 (38.3 pg/ml) at baseline for one participant, which rose to 39.6 after 3 months; but it is not clear whether the patient received antibiotic or placebo. O'Connell (2008) reported a slight increase in IL-8 from mean (SE) of 9.0 (1.1) at baseline to 10.6 (2.5) at 3 months (p=0.621, not statistically significant) for 30 participants with type 2 diabetes and periodontitis; however, the trial did not give separate values for intervention and placebo groups except to say there were no significant differences observed between treatment groups.

4. CRP

Four trials reported on CRP (Almaghlouth 2013, Lopez 2011, Payne-Golub 2011 and Tüter 2007). Almaghlouth (2013) observed peak values of CRP in four participants at baseline (values ranging from 13.4 to 52.6 µg/ml) and in three participants at 3 months (14.1 to 33.4 µg/ml); the trial authors gave no indication of how many of the participants with these peak values received antibiotics. Lopez (2011) assessed C-reactive protein (CRP) levels in participants with metabolic syndrome 82 participants received amoxicillin and metronidazole while the control group (83 participants) received placebo. Although the mean CRP levels decreased significantly at 9 and 12 months, at 3months, there were no significant differences between the two treatment groups. Payne-Golub (2011), the SDD antibiotic intervention significantly reduced median hs-CRP by 18% over a period of two years compared to the placebo the ratio of medians of SDD versus placebo (0.82, 95%CI: 0.70 to 0.97, p=0.02). Tüter, (2007) also assessed the effect of the SDD antibiotic on hs-CRP compared to placebo; however, although there were significant improvements between baseline and 6 weeks in both groups, but there was no significant difference between groups at 6 weeks (p=0.628).

5. MMP-8

Four trials reported MMP-8 (Gilowski2012; Golub-Lee 2008; Han 2012; Tüter 2007). Gilowski (2012) randomized 34 participants (17 receiving SDD and 17 receiving placebo) with chronic periodontitis and type 2 diabetes; although MMP-8 decreased significantly between baseline and three months among the SDD group while an increase was observed in the placebo group, there was no significant difference between the two groups. Golub-Lee (2008), the SDD significantly reduced the odds of increased MMP-8 levels by 60% compared to placebo during the 2-year period of study (OR 0.40, 95%CI: 0.21 to 0.77, p=0.006) among the 128 menopausal women with periodontitis (64 in each group). Han (2012), 36 participants with generalized chronic periodontitis (18 receiving azithromycin and 18 receiving placebo) showed no significant differences in GCF MMP-8 concentration between the two treatment groups from baseline to 6 months. Tüter (2007) demonstrated no significant differences in MMP-8 between the SDD and placebo group among the 36 participants with chronic periodontitis at pre- and post 6-week time points.

6. TIMP-1

One trial (Payne,Golub 2011) reported TIMP-1; there was no significant difference between the antibiotic group (SDD) and placebo group TIMP-1 among the 128 postmenopausal women with chronic periodontitis after 2 years; ratio of medians of SDD versus placebo (0.96, 95%CI: 0.78 to 1.18, p=0.7).

7. HbA1c

Eight trials reported HbA1c levels. In the study from Gaikwad (2010), there was no significant difference in HbA1c levels (%) at 4 months of treatment between the SDD and placebo groups among the 50 participants with type 2 diabetes and chronic generalized periodontitis (Mean (SD) 7.00 (0.76) SDD versus 7.11 (0.99) Placebo; p=0.710); however, the different sample sizes in each treatment group were not given at 4 months. Gilowski (2012) also found no significant difference in HbA1c (%) at 3 months after treatment with SDD compared to placebo among 34 patients with type 2 diabetes and chronic periodontitis (Median (Interquartile Range [IQR]) 6.3 (5.5,7.3) SDD versus 6.7 (6.3, 7.7) Placebo; p=0.8). Jones (2007) evaluated the effect of SDD versus placebo after 4 months of treatment among 165 veterans (83 receiving SDD antibiotic and 82 placebo) with periodontitis and poorly controlled diabetes, they found no significant difference in the percent achieving either HbA1c decreases of either > 0.5 or > 1.0 (55% versus 52% (p=0.38) or 41% versus 34% (p=0.31),

respectively). In Botero (2013), the antibiotic group had a reduction of 0.8% versus 0.3% in the placebo group; however, no comparison p-value was calculated between the two treatment groups. Also Engebretson (2011), the SDD antibiotic group (n=15) had a reduction in HbA1c levels (%) from baseline to 3 months of 0.9% versus 0% in the placebo group; however, there was no significant difference between the treatment groups (p=0.22). Grossi (1997), had 113 Native Americans with periodontal disease and type 2 diabetes participants that were randomized into three SDD groups and two placebo groups; all the three SDD groups showed significant reduction in HbA1c (%) of approximately 10% at 3 months while the placebo groups did not show significant reductions; however, no comparisons were made between the SDD and placebo groups. Miranda (2014) assessed the effect of metronidazole + amoxycillin versus placebo among 58 (29 per group) type 2 diabetic participants with periodontitis but found no significant difference in HbA1c levels (%) between the two treatment groups at baseline, 3 months, 6 months, and after 1 year of treatment (p=0.35, 0.55, 0.33, and 0.62, respectively).O'Connell 2008 found no significant difference in HbA1c (%) improvement between the SDD group (1.5%) and placebo group (0.9%) after 3 months among 30 type 2 diabetes participants with periodontitis.

SECONDARY OUTCOMES

1. Probing Depth (PD)

(a) PD (mm)

Ten trials reported probing depth (PD, in mm). A total of six trials (Almaghlouth 2013, Botero 2013, Gaikwad 2010, Miranda 2014, O'Connell 2008, Saleh 2016) measured PD (mm) at 3 months and a random effects meta-analysis of these trials yielded a significant antibiotic effect of reducing PD by 0.24 mm (Mean Difference [MD] -0.25mm, 95% confidence interval [CI]: -0.38mm to -0.12mm, n=276 participants, 6 trials,(**Analysis 1.1)**and there was no significant heterogeneity between trials (Chi^2=5.75, degrees of freedom [df]=5, p=0.33, I^2=13%). Gilowski (2012) also assessed PD (mm) at 3 months but there were no significant differences between treatment groups; the results are only reported in a figure (box and whisker plot) from which values for analysis cannot be accurately extracted. One trial (Han 2012) measured PD reduction (in mm) from baseline to 3 months and found no significant

difference between antibiotic and placebo groups (MD 0.25mm, 95% CI -0.05mm to 0.55mm (**Analysis 1.2**). One trial (Grossi 1997) reported a PD reductions at 3 months of 17%, 23%, and 22% for three antibiotic treatment groups (H_2O-doxycycline, CHX-doxycycline, and Iodine-doxycycline, respectively), compared to 15% for the placebo control group. Tüter (2007) found statistically significant improvements in PD (mm) after 6 weeks of treatment in favor of the antibiotic group compared to placebo (Median (IQR) of 3.45 (3.24 to 3.69) mm SDD versus 3.78 (3.52 to 4.2) mm Placebo, p=0.034, n=36 participants (18 per group). Miranda (2014) also assessed the antibiotic effect at 6 months and 1 year but found no significant difference between groups (data not reported).

(b) PD≤3mm

Two trials **(Botero 2013; O'Connell 2008)** measured the number of sites with PD ≤ 3mm at 3 months but found no significant difference in the mean number of sites between the antibiotic and placebo groups (MD -1, 95% CI: -22.54 to 20.53, n=98 participants, 2 trials,(**Analysis 1.3**) and there was no significant heterogeneity between trials (Chi^2=1.71, df=1, p=0.19, I^2=41%).

(c) PD≥4mm

Almaghlouth (2013) and Botero (2013) measured the number of sites with PD≥4mm after 3 months and found significantly greater reduction in the mean number of sites in favour of the antibiotic group (MD -3.38, 95% CI: -6.51 to -0.25, n=108 participants, 2 trials,(**Analysis 1.4**) and there was no significant heterogeneity between studies (Chi^2=0.01, df=1, p=0.93, I^2=0%). In Gilowski (2012), the SDD group had a significantly greater reduction in the mean number of sites with PD≥4mm (p=0.02); however the values were given in a figure from which accurate values for Mean (SD) could not be extracted. For Lopez (2011), there was a significant improvement in favor of antibiotic treatment at 3, 6, 9, and 12 months (data not reported).

2. CAL

Eight trials reported clinical attachment level (CAL). Four trials (Gaikwad 2010, Miranda 2014, O'Connell 2008, Saleh 2016) measured CAL (mm) at 3 months and a random effects meta-

analysis of these trials showed no significant difference in CAL (MD -0.13, 95% CI: -0.34 to 0.07, n=168 participants, 4 trials,(**Analysis 1.5)**; there was no significant heterogeneity between the trials (Chi^2=0.98, df=3, p=0.81, I^2=0%). Gaikwad (2010) also measured CAL (mm) at 4 months and found a significant reduction in favor of the antibiotic group (MD -0.30, 95%CI: -0.55 to -0.05, 50 participants(**Analysis 1.5)**. However, Miranda (2014) did not find significant difference between treatment groups at both month 6 (MD -0.30, 95%CI: -0.77 to 0.17, 56 participants,(**Analysis 1.5)** and month 12 (MD -0.40, 95%CI: -0.87 to 0.07, 56 participants,(**Analysis 1.5)**.

Han, (2012) measured the reduction in mean CAL (mm) but there were no significant differences between the treatment groups at month 1 (MD 0.11, 95%CI: -0.20 to 0.42, 28 patients,(**Analysis 1.6),**month 3 (MD 0.10, 95%CI: -0.28 to 0.48, 28 participants,(**Analysis 1.6),** and month 6 (MD 0.01, 95%CI: -0.36 to 0.38, 28 patients,(**Analysis 1.6).** Gilowski (2012), demonstrated there was no significant difference in CAL between groups (values only given in a figure). The Grossi (1997) trial, had three treatment groups that demonstrated CAL improvement of 12,18, and 14% at month 6 whereas the placebo group showed 6 and 9% improvement at 3 and 6 months; there were no values given to compare between intervention and control groups. Tüter (2007) found no significant difference in CAL (mm) between the antibiotic and placebo groups after 6 weeks of treatment (Median (IQR) of 3.97 (3.75 to 4.10) mm SDD versus 4.0 (3.66 to 4.46) mm Placebo, p=0.521, n=36 participants (18 per group).

3. Gingival Index (GI)

Gaikwad (2010), reported no significant difference in gingival index (GI) between the antibiotic and placebo group at month 1 (p=0.858), month 2 (p=0.252), month 3 (p=0.063), and month 4 (p=0.219); however, we could not calculate the treatment effect since the respective number of participants in each group after baseline were not given. Grossi(1997) reported that at 6 months, the antibiotic groups had a significantly greater number of participants with no detectable *P. gingivalis* compared to the control groups (data not available). Tüter (2007) reported significantly reduce GI in the antibiotic group after 6 weeks of treatment compared to the placebo group (Median (IQR) of 1.00 (0.77 to 1.16) SDD versus 1.27 (0.97 to 1.52) Placebo, p=0.027, n=36 participants (18 per group)).

4. Plaque Index (PI)

Gaikwad (2010), demonstrated no significant difference in plaque index (PI) between the antibiotic and placebo group at month 1 (p=0.459), month 2 (p=0.729), month 3 (p=0.076), and month 4 (p=0.052); however, we could not calculate the treatment effect since the respective number of participants in each group after baseline were not given. Botero (2013) measured plaque score and there was no significant difference between the antibiotic and control groups at month 3, month 6, and month 9 (**Analysis 1.7**). Grossi (1997) found significant reductions in plaque accumulation in all study groups but did not compare the antibiotic versus the placebo groups. Lopez (2011) measured the mean percent sites with plaque at 3, 6, 9, and 12 months and only found significant improvement at 12 months in favor of the antibiotic group compared to the placebo group (data was in graphic only). O'Connell (2008) found no significant difference in PI percent reduction at 3 months between the antibiotic and placebo groups (MD 8.60, 95%CI: -3.40 to 20.60, 30 participants,(**Analysis 1.8).** Saleh (2016) found no significant difference in full mouth plaque score (FMPS [%]) at 3 months between the antibiotic and placebo groups (MD -7.95, 95%CI: -21.75 to 5.85, 32 participants, (**Analysis 1.9)**. Tüter (2007) found no significant difference in PI between the antibiotic and placebo groups after 6 weeks of treatment with SDD (Median (IQR) of 0.55 (0.17 to 1.0) versus 0.75 (0.23 to 0.92) in the control group;, p=0.696, n=36 participants (18 per group).

TABLE 2: ANTIBIOTICS VERSUS NO ANTIBIOTIC/PLACEBO -ANALYSIS

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 PD (mm) at 3 months	6	276	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.38, -0.12]
1.2 PD Reduction (in mm) from baseline to 3	1	28	Mean Difference (IV, Random, 95% CI)	0.25 [-0.05, 0.55]

months				

1.3 Number of sites with PD ≤ 3mm at 3 months	2	98	Mean Difference (IV, Random, 95% CI)	-1.00 [-22.54, 20.53]
1.4 Number of sites with PD≥4mm at 3 months	2	108	Mean Difference (IV, Random, 95% CI)	-3.38 [-6.51, -0.25]

1.5 CAL (mm)	4	330	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.37, -0.08]
1.5.1 Month 3	4	168	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.34, 0.07]
1.5.2 Month 4	1	50	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.55, -0.05]
1.5.3 Month 6	1	56	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.77, 0.17]
1.5.4 Month 12	1	56	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.87, 0.07]
1.6 Reduction in mean CAL (mm)	1	84	Mean Difference (IV, Random, 95% CI)	0.08 [-0.12, 0.28]
1.6.1 Month 1	1	28	Mean Difference (IV,	0.11 [-0.20,

			Random, 95% CI)	0.42]
1.6.2 Month 3	1	28	Mean Difference (IV, Random, 95% CI)	0.10 [-0.28, 0.48]
1.6.3 Month 6	1	28	Mean Difference (IV, Random, 95% CI)	0.01 [-0.36, 0.38]

1.7 Plaque score	1	191	Mean Difference (IV, Random, 95% CI)	2.71 [-2.60, 8.02]
1.7.1 3 Months	1	68	Mean Difference (IV, Random, 95% CI)	2.47 [-5.97, 10.91]
1.7.2 6 Months	1	64	Mean Difference (IV, Random, 95% CI)	0.10 [-9.58, 9.78]
1.7.3 9 Months	1	59	Mean Difference (IV, Random, 95% CI)	5.60 [-4.03, 15.23]
1.8 PI percent reduction at 3 months	1	30	Mean Difference (IV, Random, 95% CI)	8.60 [-3.40, 20.60]

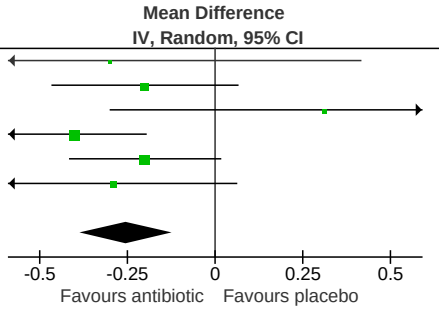
1.9 FMPS (%)	1	32	Mean Difference (IV, Random, 95% CI)	-7.95 [-21.75, 5.85]

TABLE 3: FOREST PLOTS FOR MECHANICAL DEBRIDEMENT COMBINED WITH ANTIBIOTICS IN THE TREATMENT OF PERIODONTITIS: EFFECT ON SYSTEMIC BIOMARKERS

PD at 3 months (mm)

	Antibiotic			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Almaghlouth 2013	2.6	1	19	2.9	1.3	21	3.2%	-0.30 [-1.02, 0.42]
Botero 2013	2.3	0.6	32	2.5	0.5	36	20.3%	-0.20 [-0.46, 0.06]
Gaikwad 2010	3.16	1.54	25	2.85	0.2	25	4.4%	0.31 [-0.30, 0.92]
Miranda 2014	2.6	0.2	29	3	0.5	27	31.2%	-0.40 [-0.60, -0.20]
O'Connell 2008	1.9	0.3	15	2.1	0.3	15	28.4%	-0.20 [-0.41, 0.01]
Saleh 2016	3.04	0.2	22	3.33	0.55	10	12.4%	-0.29 [-0.64, 0.06]
Total (95% CI)			**142**			**134**	**100.0%**	**-0.25 [-0.38, -0.12]**

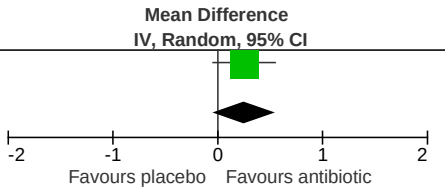
Heterogeneity: Tau² = 0.00; Chi² = 5.75, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 3.82 (P = 0.0001)



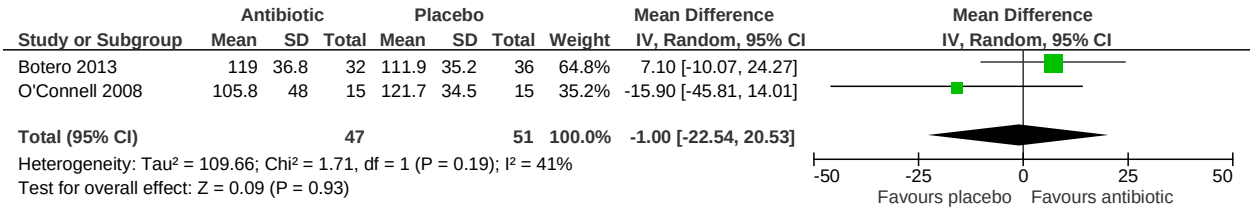
PD Reduction from Baseline to 3 months (mm)

	Antibiotic			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Han 2012	1.79	0.4	14	1.54	0.4	14	100.0%	0.25 [-0.05, 0.55]
Total (95% CI)			**14**			**14**	**100.0%**	**0.25 [-0.05, 0.55]**

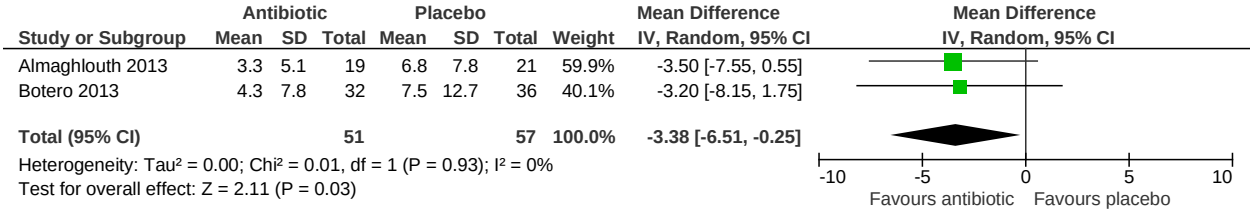
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)



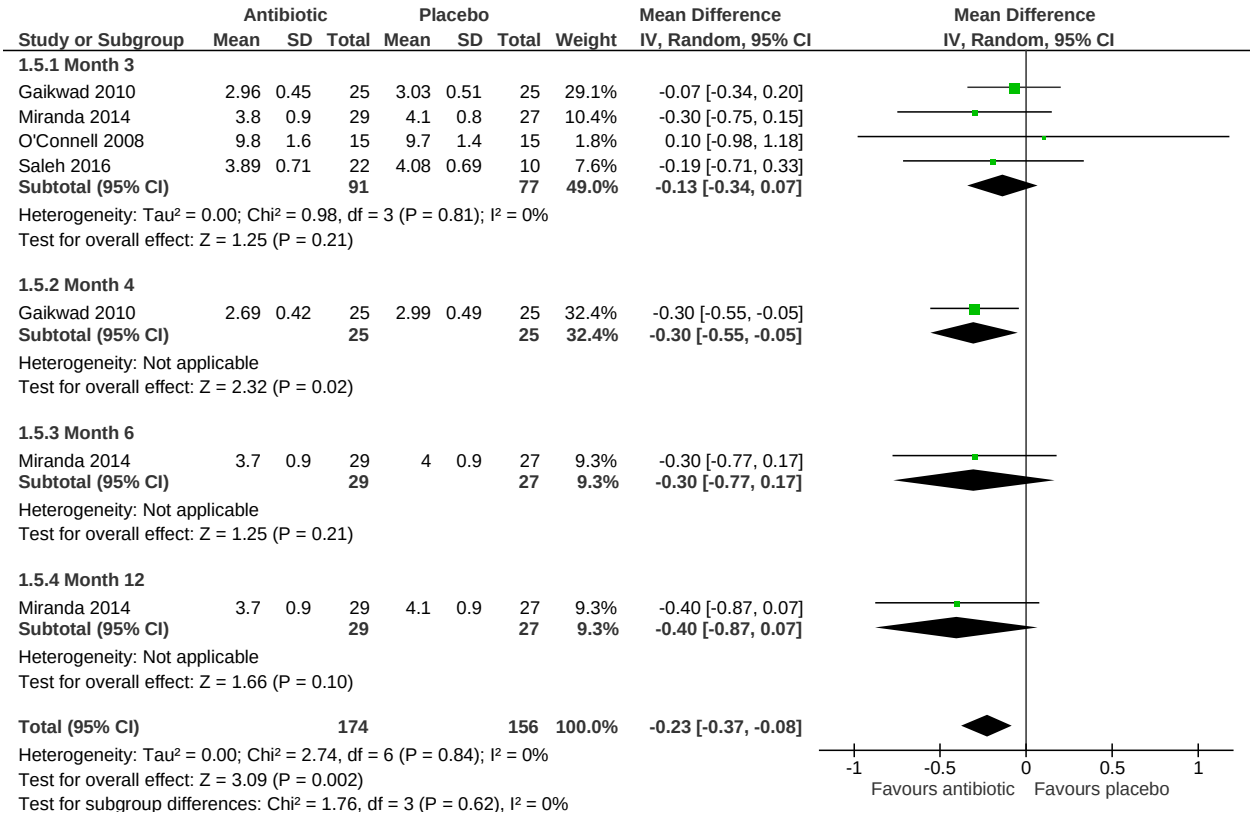
Number of sites with PD ≤ 3mm at 3 months



Number of sites with PD ≥ 4mm at 3months



CAL (mm) measurements at months 3, 6, 8 & 12



DISCUSSION

SUMMARY OF MAIN RESULTS

The primary objective of this study was to assess the effectiveness of systemic antibiotics as an adjunctive therapy to mechanical debridement in the changes of inflammatory systemic biomarkers as compared to mechanical debridement alone in chronic periodontitis. We included 14 trials consisting of 1457 participants in the analysis for this review.

The trials compared antibiotics versus placebo or no antibiotic, with mechanical debridement in either arm of the intervention. The participants in the trials included healthy individuals, menopausal women and patients with co-morbidities such as type2 diabetes and CVD. Three

studies reported no significant difference in the level of GCF IL-1β between the two treatment groups. At the 3-month follow-up, the probing depth (PD) of periodontal pockets≥4mm revealed significant decrease. The CAL, GI and PI showed negligible improvement. Adjunctive administration of antibiotics for a minimum of 3 months also showed substantial improvement on the clinical parameters of PD as compared to mechanical debridement alone. SDD demonstrated a significant reduction (60%) in the odds of increased MMP-8 levels compared to placebo during the 2-year period of study. A significant reduction in MMP-8 level was observed in type 2 diabetes at baseline and at the 3-month follow-up in the treatment group. However, there was no significant difference between the two groups. TIMP-1 levels are inversely linked to MMP-8 levels. Although there were no significant differences between the antibiotic group and placebo groups, one trial demonstrated a significant increase in saliva and GCF of TIMP-1 concentration after initial periodontal treatment in healthy participants.

Relapse data: Some of the studies show some regression in the course of the study. Botero (2013), observed a relapse in the test group (Az-Prof) and placebo group (Pb-Sca) at 6 and 9 months regarding the HbA1c levels. However, there was no relapse in the test group Az-Sca at 6 and 9 months. Details of the relapse were not reported.

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

Due to the poorly recorded methodological rigour and reporting of data, it is difficult to assess the applicability of those results. Overall, there is insufficient evidence to make general conclusions on the effects of adjunctive antibiotics on systemic biomarkers in the treatment periodontitis.

QUALITY OF THE EVIDENCE

The overall quality of evidence on primary outcomes (changes in serum/blood levels of inflammatory biomarkers such as MMPs, TIMPs, Cytokines, CRP and HbA1c) was low due to "unclear" risk of bias/ high risk of bias. Twelve of the included trials in this review lacked methodological rigour and results were not explicitly reported. Two trials (Miranda 2014; Saleh 2016) had low risk of bias, a number of the trials were not amenable to meta-analysis due to insufficient data while others did not indicate whether the reported values were for the effect of intervention in the treatment group or the placebo group. Some of the results were presented in box and whisker plots (Almaghlouth 2013; Golub,Lee 2008; O'Connell 2008)

making data extraction for analysis difficult. Only one of the four trials on CRP demonstrated a significant reduction (18%) over 2-years in the treatment group. MMP-8 demonstrated a significant difference in 1 trial, while IL-6 level was non-significant after 3 months. The HbA1c levels displayed non-significant differences between treatment groups. We used GRADE Profiler (GRADEpro 3.6) software to assess the quality of evidence on HbA1c, MMP-8, CRP and probing depth at 3 months (PD) by rating the quality of evidence, see Summary of findings table. We decided to downgrade by 1, for imprecision and risk of bias because of the wide confidence interval and loss to follow up in the studies (Attrition bias). Grading of the evidence considers factors such as study limitations, imprecision, inconsistency, indirectness of results and selective reporting (Guyatt2011). The quality of evidence for the selected outcomes was “low” suggesting that further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the presented estimate.

POTENTIAL BIASES IN THE REVIEW PROCESS

Attempts were made to minimise potential bias in this review in several ways. We conducted a comprehensive and exhaustive trial search to identify trials for inclusion in this review. We included published and unpublished trials in all languages, study search result records were screened in duplicate and all decisions on inclusion of each trial was confirmed by a third review author. As far as possible, we adhered to the agreed standardised data extraction format with at least two review authors assessing the quality, accuracy and consistency of the content according to the original articles. We cross checked references of existing literature to ensure that the previously identified studies were appraised for inclusion in this review. Authors of studies were contacted when more information was required to make explicit judgement, however not all authors responded. At least two review authors independently scrutinised and selected trials for inclusion in the review using eligibility criteria, assessed risk of bias, and extracted data. Risk of bias judgments and decision was explicitly done using the risk of bias table and graph. GRADEpro software was used to assess the quality of evidence, subjective judgement and decisions on risk of bias was done explicitly with the aid of risk of bias table.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

This is a systematic review on the effect of adjunctive antibiotic on systemic biomarkers in the treatment of chronic periodontitis. The intervention produced a mean reduction in probing depth (PD≥4mm) of 3.38mm in the periodontal pockets in the SRP+antibiotic group after 3 months in 2 trials (Almaghlouth 2013; Botero 2013). Those were included in a meta-analysis, which showed an effect estimate as MD -3.38 with 95% CI -6.51 to -0.25 (p=0.93).

The meta-analysis favoured combined SRP with systemic antibiotic therapy in terms of reduction of inflammatory markers, as it indicated inflammatory changes. These findings are supported by Polimeni (2006) who concluded that clinical attachment gains are the result of the resolution of inflammation, bone filling and the formation of long junctional epithelium.

The mean reduction in probing depth (PD) concurs with the synergistic effect of antibiotics together with SRP. Xiao & Graves (2015) stated that antibiotics improve periodontal healing whilst having a bacteriostatic effect on the target microbial species along with mechanical debridement, which in turn strengthens the immune system. Furthermore, Grellmann (2016) and Kolakovic (2014) reported that PD is more likely to show a significant reduction with antibiotic therapy in periodontal treatment than CAL. However, the study by Haffajee (2003), a systematic review of 29 trials (36 comparisons) assessed the effect of local and systemic antibotics in the treatment of periodontitis. The review by Haffajee (2003) reported a gain in the clinical attachment level and a reduction in pocket depth (PD). Herrera et al.(2002) is another systematic review which examined the effect of antibiotics on both aggressive and chronic periodontitis, the authors reported on CAL and PPD. Additionally, Ashley (1999), Caton (2000), Caton (2001), Choi (1994), Crout (1996), Emingil (2004), Gorska (2006), Novak (2002) and Lee (2004) concluded that antibiotic administration improves PD and CAL values in periodontitis.

The current review agrees with Chen (2000), Gorska (2006) and Makela (1994) that systemic antibiotic decreases the **MMP** levels in the treatment of chronic periodontal disease.

Also, the significant increase in GCF of **TIMP-1** agreed with Hayakawa et al.(1994) who confirmed a significant increase in saliva and GCF of TIMP-1 concentration after initial periodontal treatment with systemic antibiotics.

The **CRP** biomarkers in the included trials were not amenable to meta-analysis. In support of the findings from this review, which was the reduction in CRP levels after therapy in Lopez (2011), Payne (2011) and (Tüter 2007), Mattila (2002) measured the CRP and fibrinogen levels in 35 patients with adult periodontitis where the authors reported that adjunctive antibiotics decreased CRP levels. Mattilla (2002) concluded that only "susceptible" individuals react to periodontitis with an increase in CRP and the susceptible individuals may not necessarily have a severe form of the disease. In such individuals, treating periodontitis lowers the CRP levels and possibly reduced their CHD risk. Matilla (2002) postulated that an elevated CRP in periodontal disease may be individual-specific or genetically specific. The **IL-6** biomarker analysis included 3 trials which were not amenable to meta-analysis. All 3 trials revealed non-significant differences between treatment groups after 3 months. Brown (2004), demonstrated decreased IL-6 levels at 6 months in the SDD treated patient, however, the placebo treated patients did not show significant differences. Overall, there was a 32% reduction in IL-6 levels. It must be noted that Brown (2004) was a pilot RCT and was not powered to detect a difference in clinical endpoints.

IL-6 and CRP are closely associated (Brown 2004). IL-6 induces the production and release of CRP. The SDD therapy thus reduced IL-6 and CRP and this may have been due to IL-6 being inhibited upstream. In this study, the CRP was reduced by 46% in the SDD group whereas there was no significant reduction in the placebo group.

Choi (2004) reported no significant differences in the 1L-6 levels due to SRP+SDD use. Non-significant differences were observed in the **IL-1β** biomarker between the treatment groups at 3 months. However, Cazalis (2008) reported a significant decrease ($P<0.05$) in the secretion of IL-1β, IL-6, IL-8 & TNF-α and Goutoudi (2004), reported a decreased IL-1β level after SRP alone ($P<0.01$).

The **HbA1c** biomarker demonstrated a significant difference in the experimental group which was supported by Stewart (2001). The results yielded were a 17.1 and 6.7% reduction in the HbA1c levels in the treatment and control groups respectively. However, Promsudthi (2005) reported a non-significant reduction in HbA1c levels after 3 months.

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IMPLICATIONS FOR PRACTICE

The limited available evidence shows that adjunctive administration of antibiotics for a minimum of 3 months improve PD clinical parameters substantially compared to mechanical debridement alone. Similarly, the extendedtwo-year duration of adjunctive SDD with mechanical debridement shows an improvement in the systemic CRP and MMPs serum levels.

IMPLICATIONS FOR RESEARCH

The included trials reported on the following outcomes: serum/blood levels of MMPs, TIMPs, Cytokines, CRP, IL-1β, IL-6, IL-8, CRP, HbA1c, PD and GI. Further rigorous and well conducted large randomised controlled trials of high quality would be beneficial to assess the effect of adjunctive antibiotics administration on systemic biomarkers in chronic periodontitis. Majority of the included trials are of poor methodological quality and the results were portrayed in figures/illustrations, making it difficult to extract the data accurately. This limits the applicability of the result in clinical evidence-based practice.

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CONTRIBUTIONS OF AUTHORS

Sudhir Munasur (SM) and Eunice Turawa (ET) developed the protocol and Usuf Chikte (UMEC) provided the initial conceptual framework of the study comments on the draft. SM and ET screened abstracts, selected studies for inclusion, assessed the risk of bias and extracted the data. SM, ET and AM performed the data analysis and interpreted results. SM, ET and AM wrote the discussion and conclusion. UMEC provided input into all sections. All authors have seen and approved the final manuscript.

DECLARATIONS OF INTEREST

Sudhir Munasur: none known

Eunice Turawa: none known.

Alfred Musekiwa: none known.

Usuf Chikte: none known.

CHARACTERISTICS OF STUDIES

Characteristics of included studies

ALMAGHLOUTH 2013

Methods	Study design: Randomised controlled trial Trial duration: 3 months Trial location: School of Dental Medicine of the University of Geneva, Switzerland
Participants	Number of participants: 40 healthy participants with moderate-to-advanced periodontitis or patient seeking routine dental check-up, aged 25 -70 years. Presence of at least 4 teeth with a probing pocket depth (PD) of >4mm, clinical attachment loss of at least 2mm, and radiographic evidence of bone loss. (April 2009 and August 2011) Intervention group: 19 participants Control group: 21 participants.
Interventions	Intervention: 500mg Metronidazole+ 375mg Amoxicillin three times a day for 7 days. Supragingival plaque & calculus removed and oral hygiene instructions given.

	Periodontally diseased teeth were SRP-treated to the depth of the pocket under local anaesthesia Ultrasonic instruments & Gracey curettes used and pockets irrigated with 0.1% aqueous solution of chlorhexidine. Mouth rinse for next 10 days with 0.2% Chlorhexidine. SRP completed within 48 hours & 2 sessions were required for each participant. Control: Supragingival plaque & calculus removed and oral hygiene instructions given. Periodontally diseased teeth were SRP-treated to the depth of the pocket under local anaesthesia. Ultrasonic instruments & Gracey curettes used and pockets irrigated with 0.1% aqueous solution of chlorhexidine. Mouth rinse for next 10 days with 0.2% Chlorhexidine. SRP completed within 48 hours & 2 Sessions were required for each participant.
Outcomes	Primary outcomes: Changes in circulating IL-1β, IL-6, IL-8 and CRP after therapy, with or without antibiotics Secondary outcomes: Probing pocket depth/probing depth (PPD/PD)
Notes	The study was supported by Swiss National Foundation

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "Computer generated code allocation was used"
Allocation concealment (selection bias)	Low risk	Quote: "Computer-generated randomization list was concealed to the patient, the clinical examiner and the Therapist"
Blinding of participants and personnel (performance bias)	Low risk	Participants were masked, the dentist,dental technician and dental assistant were masked
Blinding of outcome assessment (detection bias)	Unclear risk	It was not reported whether the assessor was masked or not
Incomplete outcome data (attrition bias)	Low risk	All randomised participants were included in the final analysis
Selective reporting (reporting bias)	High risk	In the case of IL-6, it is not clear whether the patient was receiving antibiotic or placebo -OR- there was no indication of how many of the patients having peak values received antibiotics.
Other bias	Low risk	Non-significant

BOTERO 2013

Methods	Study design: Randomised clinical trial

	Trial duration: January 2011 to July 2012 Trial location: San Vicente de Paul Hospital Medeliin, Coloumbia.
Participants	Number of participants: 105 participants, 3-arms. Adults diagnosed with moderate periodontitis + type 1 and type 2 diabetes for duration of 2 years and above. Minimum of 10 teeth present. Moderate periodontitis was defined as 2 or more inter-proximal sites with clinical attachment level of 4mm or more not on the same tooth, or 2 or more inter-proximal sites with probing depth of 5mm or more, not on the same tooth. Non-surgical therapy(NSPT)+ Azithromycin(AZ)- [AZ-Sca] = 33 Azithromycin + Prophylaxis - [AZ-Pro] = 35 Non-surgical therapy(NSPT)+Placebo - [AZ-PbSca] = 37
Interventions	Interventions: Group #1: (AZ-Sca Group): Subgingival scaling with an ultrasonic device till smooth root surface. Polishing after supragingival scaling. Azithromycin tablet 500mg daily for 3 days consecutive days from the day of the intervention. Group #2: (AZ-Pro): Supragingival prophylaxis Azithromycin tablet 500mg daily for 3 days since intervention date. Subgingival scaling at the end of the study. Control Group: (PB-Sca Group): Subgingival scaling with an

	ultrasonic device till smooth root surface. Polishing after supragingival scaling. Placebo-tablet 1 daily for 3 days since intervention date.
Outcomes	Primary outcomes: Changes in the circulating glycosylated haemoglobin level (HbA1c). Secondary outcomes: Probing depth (PD) and plaque scores.
Notes	The name of the placebo was not provided

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated table with permutations in block of 4 was used. It was stratified by gender.
Allocation concealment (selection bias)	Low risk	Opaque, sealed and coded envelope used to conceal the assignment.
Blinding of participants and personnel (performance bias)	Low risk	Participants: Blinded, Dentist / dental technician/dental assistant blinded to the type of pharmacological treatment.
Blinding of outcome	Low risk	Method used to conceal the assignment from outcome

assessment (detection bias)		Assessor was not described (but the assessor was blinded as per study).
Incomplete outcome data (attrition bias)	Unclear risk	Loss to follow-up was described adequately. The loss to follow-up from each group was described as follows - AZ-Sca group = 5 participants (15%); AZ-Pro group = 4participants (11%) and PB-Sca group = 6 (16%)
Selective reporting (reporting bias)	High risk	In the case of HbA1c, no comparison p-value was calculated between the two treatment groups.
Other bias	Unclear risk	The authors did not provide information whether the opaque envelope was sequentially numbered to ensure adequate concealment.

ENGEBRETSON 2011

Methods	Study design: Randomised controlled trial Trial duration: 3 months Trial location: Naomi Berrie Centre and Department of Periodontics, Columbia University Medical Centre, USA.
Participants	Number of participants: 45 Type 2 diabetic individuals with untreated chronic periodontitis seeking routine maintenance visits with physician, aged 50-56 years. Type 2 diabetes diagnosed 6 months previously. Intake of prescribed oral medications or insulin for at least 3 months. Loss of clinical attachment >5mm in at least one site in each jaw quadrant. Intervention group 1: 15 participants

	Intervention group 2: 15 participants Control group: 15 participants.
Interventions	Interventions: Group #1: 20mg SDD b.i.d x 3 months. Full-mouth scaling and root planing with curettes and ultrasonic instruments under local anaesthesia for 2 hours. Blood and clinical parameters collected at 1 month and 3 months respectively. Group #2: 100mg ADD daily x 3 months. Full-mouth scaling and root planing with curettes and ultrasonic instruments under local anaesthesia for 2 hours. Blood and clinical parameters collected at 1 month and 3 months respectively. Control Group: Placebo daily x 3 months. Full-mouth scaling and root planing with curettes and ultrasonic instruments under local anaesthesia for 2 hours. Blood and clinical parameters collected at 1 month and 3 months respectively.
Outcomes	Primary outcomes: Changes in the circulating glycosylated haemoglobin level (HbA1c) Secondary outcomes: PD, Clinical attachment loss (CAL) and percentage sites with plaque were measured at baseline only and no data was provided for 3 or 6 months post-baseline.

Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment by way of computer-generated table
Allocation concealment (selection bias)	Low risk	Tablets given to all the groups were visually indistinguishable and vials were numbers with unique codes.
Blinding of participants and personnel (performance bias)	Unclear risk	Participants: Blinded Dentist/dental technician/dental assistant were not described to be blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not reported whether the assessor was masked or not, even though the study was claimed to be double-blinded.
Incomplete outcome data (attrition bias)	High risk	1/45 patients withdrew, but we do not know from which arm. Lost to follow-up: Group A: n=6; Group B: n=1; Group C: n=3.

Selective reporting (reporting bias)	Unclear risk	For the Secondary outcomes, no post baseline data at 3 or 6 months was available for PD, CAL and percentage sites with plaque.
Other bias	Low risk	Non-significant

GAIKWAD 2010

Methods	Study design: Randomised clinical trial Trial duration: 3 months Trial location: Department of Periodontics, Tatyasaheb Kore Dental College, India.
Participants	Number of participants: 50 diabetic individuals with chronic generalised periodontitis receiving antidiabetic therapy aged 30 -70 years. Probing depth of the Test group at baseline was 3.36 ± 0.35mm while the Control group was 3.34 ± 0.40mm. Clinical Attachment Level for Test group at baseline was 3.62 ± 0.50mm while that of the Control group was 3.46 ± 0.46mm. Intervention group: 25 participants. Control group: 25 participants.
Interventions	Intervention: 100mg Doxycycline once daily for 15 days. Full-mouth SRP. Periodontal measurements recorded by a single

	examiner with University of North Carolina 15 probe. No changes to diabetes medication or diet during the study. Control: No Placebo. Full-mouth SRP. Periodontal measurements recorded by a single examiner with University of North Carolina 15 probe. No changes to diabetes medication or diet during the study.
Outcomes	Primary outcomes: Changes in the circulating glycosylated haemoglobin level (HbA1c). Secondary outcomes: Reduction in probing depth (PD), Increase in Clinical attachment level (CAL).
Notes	No Placebo was given to the control group.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was not reported if there was any computer-generated code allocation.
Allocation concealment (selection bias)	Unclear risk	It was not reported if there was any allocation concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported.

Blinding of outcome assessment (detection bias)	Unclear risk	Not reported.
Incomplete outcome data (attrition bias)	Low risk	An attrition of 8 subjects was reported, hence only 42 subjects completed the study.This is 19% which is more than 15% and hence undesirable.
Selective reporting (reporting bias)	Unclear risk	In the case of HbA1c, different sample sizes for each treatment group were not given at 4 months.
Other bias	Unclear risk	non-significant

GILOWSKI 2012

Methods	Study design: Randomised controlled trial Trial duration: 3 months Trial location: Medical University of Silesia, Katowice, Poland.
Participants	Number of participants: 34 type 2 diabetic patients with severe to moderate, localized or generalized chronic periodontitis, aged 36 - 68 years in good physical condition. Diabetes diagnosed at least 6 months before the study. Presence of at least 14 teeth and a minimum of 4 non-adjacent sides with probing depth (PD) of ≥4mm. Intervention group: 17 participants

	Control group: 17 participants.
Interventions	Intervention: 20mg doxycycline hydrochloride three times a day for 3 months. NSPT, full-mouth SRP completed in 1 visit with a combination of ultrasonic and hand instruments. Local or topical anaesthesia as required. Oral hygiene instruction + tooth brushing, interdental flossing or brushing demonstrations. Control: NSPT, full-mouth SRP completed in 1 visit with a combination of ultrasonic and hand instruments. Local or topical anaesthesia as required. Oral hygiene instruction + tooth brushing, interdental flossing or brushing demonstrations.
Outcomes	Primary outcomes: Changes in circulating HbA1c and MMP-8 levels after therapy, with and without antibiotics. Secondary outcomes: CAL and PD were measured but portrayed in figures and hence could not be extracted accurately.
Notes	Name of the placebo: Saccharum lactis; PPH Galfarmsp.z.o.o., Krakow, Poland

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization was used but no mention of computer-generated randomisation.

Allocation concealment (selection bias)	Low risk	The assignment of drug containers/drugs did not include the investigators in the process.
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All study personnel and participants were blinded to the treatment assignment for the duration of the study".
Blinding of outcome assessment (detection bias)	High risk	Quote: "The statisticians and data monitoring committee saw the unblinded data".
Incomplete outcome data (attrition bias)	Unclear risk	The number of participants for each analysis was not ascertainable as it was not stated.
Selective reporting (reporting bias)	Unclear risk	In the case of Secondary outcomes, CAL and PD were measured but the data was in figures and not numerical tabulations.
Other bias	Low risk	Non-significant.

GOLUB, LEE 2008

Methods	Study design: Randomised controlled trial Trial duration: 3 months Trial location: University of Nebraska Medical Centre College of Dentistry and the School of Dental Medicine at Stonybrook University, Stoney Brook. (Multi-Centre).
Participants	Number of participants: 128 Osteopenic post-menopausal females

	with moderate to advanced periodontitis between the ages of 45-70 years, post-menopausal for at least 6 months and not receiving HRT. Good general health without co-morbidities, are having at least 9 posterior teeth and at least 2 sides with a probing depth of ≥5mm together with bleeding on probing, ≥5mm clinical attachment level loss and radiographic evidence of alveolar bone height loss. Osteopenia of the lumbar spine or femoral neck. Intervention group: 64 participants Control group: 64 participants.
Interventions	Intervention: 20mg Sub-antimicrobial dose doxycycline, three times a day for 2 years. Calcium and vitamin D supplements twice daily (a total of 1200mg of calcium and 400iu of vitamin. Periodontal maintenance consisting of scaling and root-planing every 3-4 months for 2 years. Control: 20mg Placebo, three times a day for 2 years. Calcium and vitamin D supplements twice daily (a total of 1200mg of calcium and 400iu of vitamin. Periodontal maintenance consisting of scaling and root-planing every 3-4 months for 2 years. Intervention group: 64 participants. Control group: 64 participants.
Outcomes	Primary outcomes: Changes in the GCF biomarkers IL-1ß and MMP-8 levels after therapy, with or without antibiotics. Secondary outcomes: n/a (no measurements)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization was reported but not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported neither described.
Blinding of participants and personnel (performance bias)	Low risk	Participants were masked; the dentist, dental technician and dental assistant were masked.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not reported whether the assessor was masked or not.
Incomplete outcome data (attrition bias)	Low risk	15 participants dropped out of the trial. 2 participants dropped out of the control group and 13 participants dropped out of the test group. This was 11% which was not significant.
Selective reporting (reporting bias)	Low risk	All specified outcomes were reported on.
Other bias	Unclear risk	Non-significant.

GROSSI 1997

Methods	Study design: Randomised controlled trial Trial duration: 6 months Trial location: Periodontal Disease Research Center, Department of Oral Biology, School of Dental Medicine, Buffalo, NY, USA
Participants	Number of participants: 113 participants, 5-arms. Patients suffering from moderate to severe periodontal disease with a history of diabetes mellitus as per the W.H.O. criteria. Diabetes Mellitus, diagnosed with the Haemoglobin A1c test where the HbA1c values range from ≥7% at the time of screening while that for severe periodontitis was >30% of the sites with ≥5mm clinical attachment level (CAL) and ≥2 sites with a probing depth (PD)≥6mm in each quadrant that had bleeding on probing (BOP).
Interventions	(TG1) Water irrigant + 100mg Doxycycline=22 (TG2) 0.12% Chlorhexidine irrigant + 100mg Doxycycline=23 (TG3) 0.05% Povidone-iodine irrigant + 100mg Doxycycline=23 (TG4) 0.12% Chlorhexidine irrigant + 100mg Placebo=22 (TG5) Water irrigant + 100mg Placebo=23 Group #1: Ultrasonic bactericidal curettage (UBC) performed with ultrasonic device with continuous irrigation with WATER solution where each tooth was scaled, and root planed. UBC delivered in 2 sessions, one week apart, half of the mouth treated at each session. 100mg doxycycline per day was prescribed for 2 weeks from first day of treatment. Group #2: UBC performed with ultrasonic device with continuous

	irrigation with 0.12% Chlorhexidine solution where each tooth was scaled, and root planed. UBC delivered in 2 sessions, one week apart, half of the mouth treated at each session. 100mg doxycycline per day was prescribed for 2 weeks from first day of treatment. Group #3: UBC performed with ultrasonic device with continuous irrigation with 0.05% Povidone-iodine solution where each tooth was scaled, and root planed. UBC delivered in 2 sessions, one week apart, half of the mouth treated at each session. 100mg doxycycline per day was prescribed for 2 weeks from first day of treatment. Group#4: UBC performed with ultrasonic device with continuous irrigation with 0.12% Chlorhexidine solution where each tooth was scaled, and root planed. UBC delivered in 2 sessions, one week apart, half of the mouth treated at each session. 100mg Placebo per day was prescribed for 2 weeks from first day of treatment. Control Group: UBC performed with ultrasonic device with continuous irrigation with WATER solution where each tooth was scaled, and root planed. UBC delivered in 2 sessions, one week apart, half of the mouth treated at each session. 100mg Placebo per day was prescribed for 2 weeks from first day of treatment.
Outcomes	Primary outcomes: Changes in circulating glycosylated haemoglobin levels (HbA1c). Secondary: PD and CAL were measured but the data could not be accurately extracted since they appeared in figures and not tabulations.
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method used for randomisation was not stated.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	No information provided whether the Dentist, Dental Technician or Dental assistant was blinded.
Blinding of outcome assessment (detection bias)	Low risk	Clinical assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	There was no loss to follow-up. However, 4 patients were excluded at analysis stage, 2 patients from the iodine/doxycycline group and 2 patients from the water/placebo group. The analysis was per-protocol.
Selective reporting (reporting bias)	Unclear risk	The estimates for PD and CAL at 3 and 6 months, are not reported in tabular form but in figures, while only the baseline estimates are stated in tabular form.
Other bias	Unclear risk	Non-significant

HAN 2012

Methods	Study design: Randomised clinical trial Trial duration: 6 months Trial location: Department of Periodontology, School of Dentistry, Ege University, Izmir, Turkey.
Participants	Number of participants: 36 participants. Systemically healthy patients with severe generalised chronic periodontitis in the age range of 35 – 54 years, diagnosed with severe generalised chronic periodontitis if they had >30% of the sites with ≥5mm clinical attachment level (CAL) and ≥2 sites with a probing depth (PD) ≥6 mm in each quadrant that had bleeding on probing (BOP). CAL was consistent with the amount of plaque accumulation or local contributing factors. Presence of 16 or more teeth. Intervention group: 18 participants. Control group: 18 participants.
Interventions	Intervention: 500mg Azithromycin once daily x 3 days. Oral hygiene instruction and full-mouth SRP performed per quadrant under local anaesthesia in 4 sequential visits. After SRP, GCF and subgingival plaque samples were collected. 500 mg Azithromycin was given at the end of the last treatment visit, once daily for 3 days. Motivation to reinforce the oral hygiene and maintenance therapy was administered at every visit during the study period. Control: Oral hygiene instruction and full-mouth SRP performed per quadrant under local anaesthesia in 4 sequential visits. After SRP, GCF and subgingival plaque samples were collected. 500 mg Placebo was given at the end of the last treatment visit, once daily for

	3 days. Motivation to reinforce the oral hygiene and maintenance therapy was administered at every visit during the study period.
Outcomes	Primary outcomes: Changes the GCF MMP-8 levels after therapy, with or without antibiotics. Secondary outcomes: PD sites in percentage, however, the data from baseline to 4 months was incomplete.
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list.
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed by randomization list kept by one author and medications distributed by another masked author. Medication and placebo in identical opaque capsules.
Blinding of participants and personnel (performance bias)	Low risk	Participants: Blinded, Dentist/dental technician/dental assistant blinded to the type of pharmacological treatment.
Blinding of outcome assessment (detection	Low risk	Outcome assessor was blinded, and Biostatistician was masked to treatment assignment for the study

bias)		duration.
Incomplete outcome data (attrition bias)	High risk	8 patients were excluded, 4 from each arm due to their inability to attend regular maintenance appointments. This was a 22% exclusion rate.
Selective reporting (reporting bias)	Unclear risk	In the case of Secondary outcomes, for the PD sites in percentage, the data from baseline to 4 months was incomplete.
Other bias	Unclear risk	Non-significant.

JONES 2007

Methods	Study design: Randomised controlled trial Trial duration: 4 months Trial location: All 4 Department of Veterans Administration facilities at greater Boston, United States of America. (Multi-site study).
Participants	Number of participants: 165 Diabetic veterans with poorly controlled diabetes having ≥1 HbA1c values of >8.5% within the last 6 months and they had at least 8 teeth and had sufficient periodontal treatment need as indicated by the CPITN scores of ≥3 in at least 2 sextants. Intervention group: 83 participants Control group: 82 participants
Interventions	Intervention: 100mg doxycycline daily for 14 days and chlorhexidine gluconate rinses 30cc 0.12% twice daily for 4 months.

	The intervention was *early treatment* for 4 months which consisted of periodontal scaling and root-planing until smooth root surfaces were achieved. Control: *Early treatment* for 4 months which consisted of periodontal scaling and root-planing until smooth root surfaces were achieved. Usual care was given to the control group and no medications or drugs were given to them.
Outcomes	Primary outcomes: Changes in circulating glycosylated haemoglobin (HbA1c) in the early treatment versus untreated (usual care) groups and percent of participants with decreases in HbA1c. Secondary outcomes: Periodontal pocket depth (PPD) sites in percentage, however the data from baseline to 4 months was incomplete and hence unworkable.
Notes	This is a multi-centre trial.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The Proc Plan in SAS version 8 software was used to obtain 12 blocks of 8 using a seed of 020348.
Allocation concealment (selection bias)	Low risk	Group assignments were put on a white card and sealed in white envelopes and numbered consecutively.

Blinding of participants and personnel (performance bias)	High risk	Participants were not masked; the dentist, dental technician and dental assistant were not masked.
Blinding of outcome assessment (detection bias)	Low risk	The outcome assessor was blinded.
Incomplete outcome data (attrition bias)	High risk	Out of 193 randomized participants, 28 were excluded and 165 were included in the study while 33 persons withdrew and finally, 132 participants completed the study. The drop-out rate was high. 32% of participants never complete the trial.
Selective reporting (reporting bias)	Unclear risk	the secondary outcomes measured were periodontal pocket depth (sites in percentage), however, the data from baseline to 4 months was incomplete and hence unworkable
Other bias	High risk	A 5% difference at baseline between Usual treatment and Early treatment group with respect to diabetes medicines, insulin only.

LOPEZ 2011

Methods	Study design: Randomised clinical trial Trial duration: 12 months Trial location: Dr. Eloisa Diaz Dental Center, San José Hospital,

	Santiago, Chile.
Participants	Number of participants: 165 participants with Metabolic Syndrome (MetS) having periodontitis, between the ages of 35 – 65 years and having retained ≥14 teeth. The diagnostic criteria for periodontitis was the presence of ≥4 teeth with ≥1 sites with probing depth (PD)≥4 mm and concomitant clinical attachment loss of ≥3mm.Intervention group: 82 participants. Control group: 83 participants.
Interventions	Intervention: 250mg Metronidazole t.i.d AND 500mg Amoxicillint.i.d for 7 days. Oral hygiene instructions were given. Supra & Subgingival SRP & crown polishing under LA with hand and ultrasonic instruments. Control: 50mg placebo t.i.d AND 500mg placebo t.i.d for 7 days. Oral hygiene instructions were given. Supra & Subgingival SRP & crown polishing under LA with hand and ultrasonic instruments.
Outcomes	Primary outcomes: Changes in circulating serum CRP levels. Secondary outcomes: PD, CAL and Plaque (percentage of sites), however, their depiction in figures could not enable accurate data extraction.
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	**Authors'**	**Support for judgement**

	judgement	
Random sequence generation (selection bias)	Low risk	Computer-generated for the first 8 participants enrolled. For the remaining participants, the Minimization method was used to assign them to the groups.
Allocation concealment (selection bias)	Low risk	Allocation sequence generated by a statistician without clinical involvement in the study, who also assigned the participants to study groups. Medication and placebo tablets were identical in appearance, in consecutively numbered bottles as per the randomization schedule. Treatment assignments concealed by opaque envelopes and group allocation revealed to the therapist on the day treatment began.
Blinding of participants and personnel (performance bias)	Unclear risk	Participants were masked; the dentist, dental technician and dental assistant were NOT masked.
Blinding of outcome assessment (detection bias)	Low risk	The outcome assessor was masked.
Incomplete outcome data (attrition bias)	Low risk	5 participants were excluded at the final analysis stage, 3 from the test group, and 2 from the control group. 3% of participants did not complete the trial.
Selective reporting (reporting bias)	Unclear risk	In the case of Secondary outcomes, the depiction of the data for PD, CAL and Plaque percentage (of sites) in figures lead to imprecise data.

Other bias	Low risk	Non-significant.

MIRANDA 2014

Methods	Study design: Randomised controlled trial Trial duration: 1 year Trial location: Department of Periodontology, Dental Research Division, Guarulhos University, Sao Paulo, Brazil.
Participants	Number of participants: 58 Type 2 diabetic participants with generalized chronic periodontitis referred to the dental clinic, aged 35 years or more. Diagnosed with type 2 DM for 5 or more years. Presence of at least 15 teeth. More than 30% of the sites with probing depth (PD) and clinical attachment level (CAL) of ≥4mm and a minimum of 6 teeth with at least 1 site with PD and CAL ≥5mm and bleeding on probing (BoP) at baseline. Intervention group: 29 participants Control group: 29 participants.
Interventions	Intervention: After 1st SRP session, 400mg Metronidazole+ 500mg Amoxycillin three times a day for 14 days. Initial supragingival plaque & calculus removal and restorations. Oral hygiene instructions given. 4-6 one hour-sessions of SRP with manual curettes and ultrasound device under local anaesthesia.

	Duration of therapy was 14 days. End-point for SRP appointment was the confirmation of smoothness of the scaled roots as checked by study co-ordinator. Control: After 1st SRP session, Placebo was dispensed. Initial supragingival plaque & calculus removal and restorations. Oral hygiene instructions given. 4-6 one hour-sessions of SRP with manual curettes and ultrasound device under local anaesthesia. Duration of therapy was 14 days. End-point for SRP appointment was the confirmation of smoothness of the scaled roots as checked by study co-ordinator.
Outcomes	Primary outcomes: Changes in the circulating glycosylated haemoglobin level (HbA1c). Secondary outcomes: Reduction in probing depth (PD) and gain in clinical attachment level (CAL).
Notes	Name of the placebo was not provided. Funding by the São Paulo State Research Foundation, Brazil.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code allocation was used.
Allocation concealment	Low risk	Identical plastic bottles containing antibiotics or

(selection bias)		placebos were coded to conceal assignment.
Blinding of participants and personnel (performance bias)	Low risk	Participants: Blinded, Dentist/dental technician/dental assistant blinded to the type of pharmacological treatment.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up was described adequately. 2 participants from control group did not attend baseline visit and were excluded.
Selective reporting (reporting bias)	Low risk	The protocol was not available, but all specified outcomes were reported on.
Other bias	Low risk	Non-significant

O'CONNELL 2008

Methods	Study design: Randomised controlled trial. Trial duration: 3 months Trial location: Department of Oral Surgery & Periodontology, University of São Paulo Ribeiro-Preto, Brazil.
Participants	Number of participants: 30 Type 2 diabetic participants in good physical condition and having no additional serious medical conditions with periodontitis recruited from 2400 medical records, aged 46-70 years. Type 2 diabetes mellitus diagnosed for >5 years

	and HbA1c>8%. Presence of at least 1 site with probing depth≥5mm and 2 teeth with attachment loss≥6mm. Intervention group: 15 participants Control group: 15 participants
Interventions	Intervention: 100mg Doxycycline once daily for 2 weeks after an initial dose of 200mg. Pre-SRP antibiotics a day before therapy. A total of 4 sessions within 24-36 hours using hand instruments and ultrasonic device under local anaesthesia. Extraction of unsalvageable teeth. Oral hygiene reviewed twice monthly followed by prophylaxis for 3 months. Control: Placebo once daily for 2 weeks after initial dose of placebo. A total of 4 sessions within 24-36 hours using hand instruments and ultrasonic device under local anaesthesia. Extraction of unsalvageable teeth. Oral hygiene reviewed twice monthly followed by prophylaxis for 3 months.
Outcomes	Primary outcomes: Changes in the circulating glycosylated haemoglobin level (HbA1c) and IL-1ß levels. Secondary outcomes: Changes in Periodontal probing depth (PD), Clinical attachment loss (CAL) and Plaque Index percent reduction (PI).
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The participants that met the inclusion criteria were assigned to two groups randomly.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias)	Unclear risk	The trial itself was double-masked, placebo-controlled.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not mentioned if the operator was blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Outcome data on subjects who did not complete treatment is not mentioned.
Selective reporting (reporting bias)	High risk	All specified outcomes were reported on though the researchers did not give separate results for the intervention and placebo groups.
Other bias	Low risk	Non-significant.

PAYNE, Golub 2011

Methods	Study design: Randomised controlled trial

	Trial duration: 2 years Trial location: University of Nebraska Medical Centre, College of Dentistry and Department of Oral Biology & Pathology School of Dental Medicine, Stoney Brook University, New York, USA.
Participants	Number of participants: 113 Post-menopausal women with osteopenic at lumbar spine or femoral neck, with generalized to advanced chronic periodontitis recruited on a rolling admission basis, aged 45-70 years. Presence of at least 2 sites with probing depths and clinical attachment loss ≥5mm together with bleeding on probing. The 2 sites had to be on different posterior teeth. Intervention group: 51 participants Control group: 62 participants.
Interventions	Intervention: 20mg SDD once daily for 2 years Periodontal maintenance therapy over a 2-year period consisting of scaling and root-planing. 1200mg Calcium and 400mg i.u. vitamin D supplements to be taken twice daily were taken 1 hour after taking study drug. Control: Placebo once daily for 2 years Periodontal maintenance therapy over a 2-year period consisting of scaling and root-planing. 1200mg Calcium and 400mg i.u. vitamin D supplements to be taken twice daily were taken 1 hour after taking study drug.
Outcomes	Primary outcomes: Changes in circulating hs-CRP, IL-6, IL-1ß, MMP-8 and TIMP-1 after therapy, with or without antibiotics. Secondary outcomes: not measured.

Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomized through a call-in centre.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not stated.
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Treatment code identifying the SDD and Placebo arms were concealed from study investigators and statistician".
Incomplete outcome data (attrition bias)	Low risk	Loss to follow-up was described adequately with 13 participants lost as follows: 13 subjects withdrew consent (placebo n=2, SDD n=10) and 1 subject withdrew due to adverse effects (SDD n=1). 11% was the loss to follow-up.
Selective reporting	Unclear risk	Secondary outcomes were not reported.

(reporting bias)		
Other bias	Unclear risk	No description given regarding allocation concealment.

REINHARDT 2010

Methods	Study design: Randomised controlled trial Trial duration: 3 years Trial location: University of Nebraska Medical Centre College of Dentistry and the School of Dental Medicine at Stonybrook University, Stoney Brook. (Multi-Centre).
Participants	Number of participants: 128 Osteopenic post-menopausal females with moderate to advanced periodontitis between the ages of 45-70 years, post-menopausal for atleast 6 months and not receiving HRT. Good general health without co-morbidities, are having at least 9 posterior teeth and at least 2 sides with a probing depth of ≥5mm together with bleeding on probing, ≥5mm clinical attachment level loss and radiographic evidence of alveolar bone height loss. Osteopenia of the lumbar spine or femoral neck. Intervention group: 64 participants Control group: 64 participants.
Interventions	Intervention: 20 mg Sub-antimicrobial dose doxycycline (SDD) three

	times daily for 2 years. Periodontal maintenance therapy every 3-4 months over a 2-year period consisting of scaling and root-planing. 1200mg Calcium and 400mg i.u. vitamin D supplements to be taken twice daily were taken 1 hour after taking the study drug. Control: 20 mg Placebo three times daily for 2 years. Periodontal maintenance therapy every 3-4 months over a 2-year period consisting of scaling and root-planing. 1200mg Calcium and 400mg i.u. vitamin D supplements to be taken twice daily were taken 1 hour after taking the study drug.
Outcomes	Primary outcomes: Changes in GCF biomarkers IL-1ß and MMP-8 after therapy, with or without antibiotics. Secondary outcomes: Changes in the relative Clinical Attachment Levels (rCAL), however, no baseline values for rCAL were reported.
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list which was generated in blocks to randomize participants to groups.
Allocation concealment	Low risk	Treatment allocation was concealed as treatment

(selection bias)		assignments were given over the telephone.
Blinding of participants and personnel (performance bias)	Low risk	Participants were masked; the dentist, dental technician and dental assistant were masked.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not reported whether the assessor was masked or not.
Incomplete outcome data (attrition bias)	Low risk	15 participants were excluded. 2 participants dropped out of the control group. 13 participants dropped out of the test group.
Selective reporting (reporting bias)	Unclear risk	In the case of Secondary outcomes, there were no baseline values for the changes in the relative clinical attachment level (rCAL).
Other bias	Unclear risk	No mention is made whether the telephone call was recorded by the call-centre for verification purposes.

SALEH 2016

Methods	Study design: Randomised controlled trial

	Trial duration: 3 months Trial location: Oral Health Centre, University of Western Australia, Australia.
Participants	Number of participants: 37 participants, 3 arms. Adults above the age of 30 and non-smokers, with generalized moderate to advanced chronic periodontitis. Good systemic health. Minimum of 20 teeth present and minimum of 8 sites with PPD≥5mm, CAL≥5mm and bleeding in probing (BOP). Radiographic evidence of bone loss of at least ⅓ of root length. Intervention #1: Scaling and root planing (SRP)+Amoxicillin+Metronidazole=13 Intervention #2: SRP+Azithromycin=12 Control group: SRP+placebo=12
Interventions	Interventions: Group #1: (Amox+MET): Oral hygiene instructions (OHI) and extraction of non-restorable teeth. Periodontal debridement in 2-4 sessions for each patient under local anaesthetic using hand and ultrasonic instruments till the scaled roots displayed smooth surfaces. At the end of the scaling and root planing (SRP) sessions, 500mg Amoxicillin and 200mg Metronidazole administered every 8 hours for 7 days. Group #2: (AZ): Oral hygiene instructions (OHI) and extraction of non-restorable teeth. Periodontal debridement in 2-4 sessions for each patient under local anaesthetic using hand and ultrasonic instruments till the scaled roots displayed smooth surfaces. At the end of the SRP sessions, 500mg Azithromycin administered every 8 hours for 7 days.

	Control Group: (SRP+Placebo): Oral hygiene instructions (OHI) and extraction of non-restorable teeth. Periodontal debridement in 2-4 sessions for each patient under local anaesthetic using hand and ultrasonic instruments till the scaled roots displayed smooth surfaces. At the end of the SRP sessions, Placebo capsules were administered every 8 hours for 7 days.
Outcomes	Primary outcomes: Changes in probing depth (PD) in mm, in clinical attachment level (CAL) and plaque index (PI). Secondary outcomes: nil
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment by means of a computer-generated table.
Allocation concealment (selection bias)	Low risk	Participants were divided randomly into 3 colour coded groups and a medication corresponding to each colour.
Blinding of participants and personnel (performance bias)	Low risk	Participants: blinded Dentist/Clinician/Assistant: blinded.

Blinding of outcome assessment (detection bias)	Low risk	Quote: "The type of medication corresponding to each colour was not revealed until the statistical analyses were complete".
Incomplete outcome data (attrition bias)	Low risk	All randomised participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	The protocol was not available, but all outcomes were addressed which was set out in the beginning.
Other bias	Low risk	Non-significant.

TÜTER 2007

Methods	Study design: Randomised clinical trial Trial duration: 6 weeks Trial location: Department of periodontology of Gazi University, Ankara, Turkey.
Participants	Number of participants: 36 participants with both chronic periodontitis and coronary artery disease (CAD), and age not > 70 years who had angiographically proven CAD. Patients showing radiographic evidence of bone loss and attachment loss and those who had a minimum of 6 periodontal pockets >4mm. Intervention group: 18 participants. Control group: 18 participants.
Interventions	Intervention: 20 mg Sub-antimicrobial dose doxycycline (SDD) three times

	daily for 6 weeks. Phase 1 therapy including oral hygiene instruction and SRP under local anaesthesia. 2. Full-mouth SRP once a week for 2 weeks by sharp sickles, Gracey & universal curettes and ultrasonic instruments. Control: 20 mg Placebo, three times daily for 6 weeks. Phase 1 therapy including oral hygiene instruction and SRP under local anaesthesia. 2. Full-mouth SRP once a week for 2 weeks by sharp sickles, Gracey & universal curettes and ultrasonic instruments.
Outcomes	Primary outcomes: Changes in the GCF levels of MMP-8 and serum levels of hs-CRP. Secondary outcomes: Plaque index (PI), Pocket probing depth (PD) and Clinical attachment loss (CAL).
Notes	The name of the placebo was not provided.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Blinding of participants and personnel (performance bias)	Low risk	Participants were masked; the dentist, dental technician and dental assistant were masked.
Blinding of outcome assessment (detection bias)	Unclear risk	It was not reported whether the assessor was masked or not.
Incomplete outcome data (attrition bias)	Low risk	All randomized participants were included in the final analysis.
Selective reporting (reporting bias)	Low risk	All specified outcomes were reported on.
Other bias	Unclear risk	Non-significant.

CHARACTERISTICS OF EXCLUDED STUDIES

Aljateeli 2014

Reason for exclusion	Surgical procedure as opposed to non-surgical therapy

Ardila 2015

Reason for exclusion	Aggressive periodontitis

Arora 2013

Reason for exclusion	Non-antibiotics in intervention-arm

Arweiler 2014

Reason for exclusion	Aggressive periodontitis

Awartani 1998

Reason for exclusion	Local application of antibiotic gel

Bogren 2008

Reason for exclusion	Aggressive periodontitis

Cionca 2009

Reason for exclusion	No relevant biomarkers

D'Aiuto 2005

Reason for exclusion	No systemic antibiotic therapy

Dastoor 2007

Reason for exclusion	Locally delivered antibiotic

Emingil 2012

Reason for exclusion	Aggressive periodontitis

Fiorini 2013

Reason for exclusion	No antibiotics in intervention-arm

Giannopoulou 2016

Reason for exclusion	Periodontal surgery performed in RCT

Goodson 2012

Reason for exclusion	No relevant biomarkers

Graziani 2015

Reason for exclusion	No antibiotics in intervention-arm

Griffiths 2011

Reason for exclusion	Aggressive periodontitis

Guerrero 2014

Reason for exclusion	Aggressive periodontitis

Haas 2008

Reason for exclusion	Aggressive periodontitis

Haas 2012

Reason for exclusion	Aggressive periodontitis

Haas 2016

Reason for exclusion	Aggressive periodontitis

Harks 2015

Reason for exclusion	No relevant biomarkers

Khader 2010

Reason for exclusion	No non-surgical periodontal therapy nor scaling and root-planing

Li 2013

Reason for exclusion	No relevant biomarkers

Lopez 1998

Reason for exclusion	No relevant biomarkers

Lopez 2000

Reason for exclusion	No relevant biomarkers

Lopez 2006

Reason for exclusion	No relevant biomarkers

Marcaccini 2010

Reason for exclusion	No antibiotics in intervention-arm

Mascarenhas 2005

Reason for exclusion	No relevant biomarkers

Mestnik 2012

Reason for exclusion	Aggressive periodontitis

Miremadi 2014

Reason for exclusion	Surgical procedure as opposed to non-surgical periodontal therapy

Mombelii 2013

Reason for exclusion	No relevant biomarkers

Mombelli 2005

Reason for exclusion	No relevant biomarkers

Mombelli 2015

Reason for exclusion	No relevant biomarkers

Monsarrat 2013

Reason for exclusion	Not an RCT

Oringer 2002

Reason for exclusion	Local delivery of antibiotics

Pourabbas 2014

Reason for exclusion	Photodynamic therapy is not non-surgical periodontal therapy.

Preshaw 2008

Reason for exclusion	No relevant biomarkers

Preus 2013

Reason for exclusion	No relevant biomarkers

Preus 2015

Reason for exclusion	No relevant biomarkers

Ramirez 2011

Reason for exclusion	Not an RCT

Renvert 2006

Reason for exclusion	Local delivery of antibiotics

Renvert 2008

Reason for exclusion	Peri-implantitis is not chronic periodontitis

Salminen 2013

Reason forexclusion	No relevant biomarkers

ADDITIONAL TABLES

TABLE 4: STUDY PARTICIPANTS AND DIAGNOSTIC CRITERIA FOR INCLUSION

Study ID	Participant status	Periodontitis assessment for inclusion
Almaghlouth 2013	Healthy individuals without medical condition	Moderate – to - advanced periodontitis. Presence of at least 4 teeth with PPD ≥4mm, CAL at least ≥2mm and radiographic evidence of bone loss.
Botero 2013	Diabetes type 1 or type 2 for duration of 2 years and above.	Moderate periodontitis Presence of 10 teeth and above. CAL ≥4mm, PD of 5mm or more.

Engebretson 2011	Type 2 diabetes diagnosed for 6 months duration	CAL ≥5mm
Gaikwad 2010	Diabetes disease on medication	Chronic periodontitis with PD 3.36mm, CAL 3.62mm
Gilowski 2012	Type 2 diabetes diagnosed at least 6 months before the study period	Periodontitis. Presence of at least 14 teeth and a minimum of 4 non-adjacent sides. PD ≥4mm
Golub 2008	Osteopenic post-menopausal women not on Hormone Replacement Therapy (HRT)	PD ≥5mm, bleeding on probe. CAL ≥5mm with radiographic evidence of alveolar bone loss
Grossi 1997	Diagnosed with diabetes mellitus	Diabetes Mellitus, diagnosed with the Haemoglobin A1c test where the HbA1c values range from ≥7% at the time of screening while that for severe periodontitis was >30% of the sites with ≥5mm clinical attachment level (CAL) and ≥2 sites with a probing depth (PD)≥6mm in each quadrant that had bleeding on probing (BOP).
Han 2012	Healthy individuals	Presence of 16 teeth or more. CAL ≥5mm and PD ≥2mm with BOP.
Jones 2007	Diabetic veterans with Hb1c >8.5% in the last 6 months before the	Presence of 8 teeth, CPITN >3 in at least 2 sextants

	trial commenced	
Lopez 2011	Metabolic Syndrome (MetS)	Minimum teeth – 14, PD ≥4mm and CAL ≥3mm
Miranda 2014	Diagnosed with type 2 diabetes for more than 5 years	Presence of at least 15 teeth, CAL ≥4mm and one site of PD and bleeding on probe
O'connell 2008	Diagnosed with type 2 diabetes for more than 5 years and Hb1c >8%	PD ≥5mm CAL ≥6mm
Payne, Golub 2011	Post-menopausal women with osteopenic at lumbar spine or femoral neck	Presence of at least 2 sites of PD and CAL ≥5mm in different site of posterior teeth
Reinhardt 2010	Osteopenic post-menopausal women not on HRT nor co-morbidity	Presence of at least 9 posterior teeth, PD ≥5mm with bleeding on probe. CAL ≥5mm and radiographic evidence of alveolar bone loss
Saleh 2016	Healthy participants	Minimum of 8 sites with PPD ≥5mm and CAL ≥5mm. BOP and radiographic evidence of bone loss of at least 1/3 of the root of the teeth.
Tuter 2007	Angiographic diagnosed coronary artery disease (CAD)	PPD ≥4mm with evidence of bone loss

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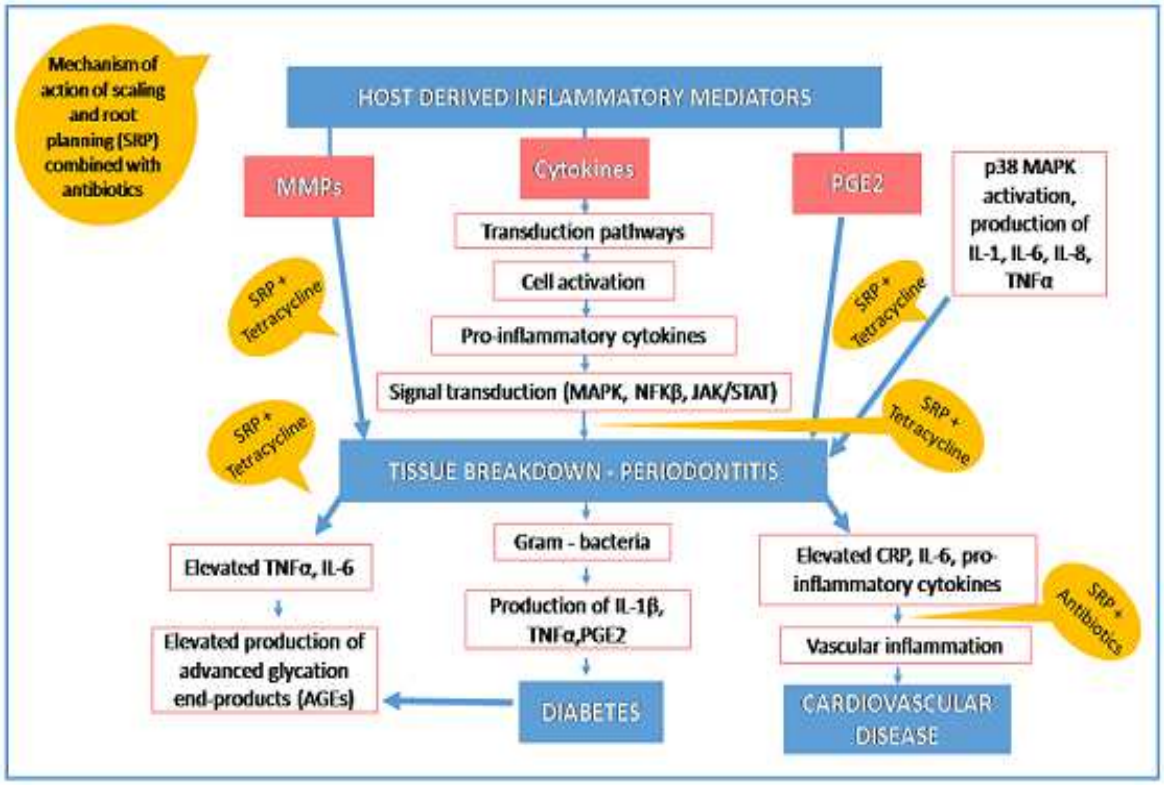

Figure 4: Effects of mechanical debridement combined with antibiotics on biomarkers. (Disruption of the inflammatory pathways by periodontal therapy)

APPENDICES

APPENDIX 1

SEARCH TERMS

(Medline/PubMed)

Anti-infective" OR "anti-infective agents" OR “anti-bacterial agents” [MH] OR “systemic antibiotics” OR “antibiotic OR "antibiotic therapy”) AND (periodontitis OR “chronic periodontitis” OR “periodontal diseases” [MH] OR “periodontitis” [MH] OR Periodontal infection).

The Cochrane Central Register of Controlled Trials (CENTRAL)

The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library is searched using MeSH terms pertaining to periodontitis and Dentistry. CENTRAL consists of details of published articles taken from bibliographic databases (MEDLINE and EMBASE amongst other databases) and various published and unpublished sources; the Specialised Registers maintained by each Cochrane Group consisting of results of the Cochrane Collaboration's global hand-searching activities. The search pertaining to the Cochcrane Library was as follows:

ID SearchHits
#1MeSH descriptor: [Periodontitis] explode all trees2583
#2MeSH descriptor: [Chronic Periodontitis] explode all trees681
#3MeSH descriptor: [Root Planing] explode all trees610
#4MeSH descriptor: [Dental Scaling] explode all trees1087
#5MeSH descriptor: [Anti-Bacterial Agents] explode all trees10848
#6MeSH descriptor: [Biomarkers] explode all trees18369

#7MeSH descriptor: [Matrix Metalloproteinase 8] explode all trees62
#8MeSH descriptor: [Glycated Hemoglobin A] explode all trees5084
#9MeSH descriptor: [Interleukin-1beta] explode all trees373
#10MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-1] explode all trees118
#11MeSH descriptor: [Interleukin-6] explode all trees2811
#12MeSH descriptor: [Interleukin-8] explode all trees761
#13MeSH descriptor: [C-Reactive Protein] explode all trees4227
#14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) in Trials with 'Oral Health' in Cochrane Groups (Word variations have been searched)2608; #15Periodont* NOT Photodynamic8882; #16Periodont* NOT Topical8550#17Periodontal NOT Laser6042; #18Periodont* NOT Gel8493; #19Periodont* NOT Irrigation8724; #20Periodontal NOT release6240; #21Periodontitis NOT Aggressive3008; #22Periodontal NOT Flap5702
#23Periodontal NOT Regeneration5616; #24Periodont* NOT Chlorhexidine8092; #25Periodontal NOT Subgingival5512; #26Periodontal NOT Osseous6182; #27Periodont* NOT Rinse8588; #28Periodontal NOT surg*3855; #29Periodont* NOT Local7818; #30Periodontal NOT toothbrush6052; #31Periodont* NOT pockets8349; #32Periodont* NOT antioxidant8965; #33(#14 AND #15 AND #16 AND #17 AND #18 AND #19 AND #20 AND #21 AND #22 AND #23 AND #24 AND #25 AND #26 AND #27 AND #28 AND #29 AND #30 AND #31 AND #32)173; #34Periodont* NOT Instrumen*7786; #35(#33 and #34)149; #36Periodont* NOT Alveolar7789; #37(#35 AND #36)134; #38Oral NOT hygiene151504; #39(#37 AND #38)113; #40Periodont* NOT pulp*8736; #41(#39 AND #40)111; #42Periodont* NOT Fluoride8575; #43(#41 AND #42)108; #44Periodont* NOT probiotic*8969; #45(#43 AND #44)105; #46Periodont* NOT diet*8846; #47(#45 AND #46)100; #48Periodont* NOT fib*8591; #49(#47AND #48)93; #50Periodont* NOT disinfect*8877; #51(#49 AND #50)91; #52Periodont* NOT lesions8623; #53(#51 AND #52)90; #54Periodont* NOT meloxicam9036; #55(#53 AND #54)88; #56Periodont* NOT flurbiprofen9006; #57(#55 AND #56)85; #58Periodont* NOT relationship8750; #59(#57 AND #58)76; #60Periodont* NOT calcium8662; #61(#59 AND #60)75

Appendix 2: Data extraction form for mechanical debridement combined with antibiotics in the treatment of periodontitis: effect on systemic biomarkers

Review ID:	**Study ID**:	**Reference ID:**
Person extracting data and date	**Date of date extraction:**	**Year of study publication:**
Title:		
Author:	**Publication type:**Full text / Abstract / Book chapter/ progress report / others.	
Country:		
Checked by:		

Study design

Type of study design (cluster RCT; block randomisation; stratified randomisation; multi-arm; factorial etc):

Unit of randomisation:

Participants and setting:

Describe setting:

Inclusion criteria:

Exclusion criteria:

PARTICIPANTS

Were the participants patients diagnosed with chronic periodontal disease?

Describe participants:

Intervention:

Were comparison groups treated with pre-specified

Intervention in one group and control intervention in the other group**?**

Experimental intervention: Type of intervention: Need to clearly describe what the intervention was all about

Comparison **Type of control used**:Active/ No therapy **Need to clearly describe what the control was all about**	
Balanced between treatment arms?	Yes / No
OUTCOMES ASSESSED: Definition of outcome assessed: Primary outcomes Secondary outcomes Outcome not specified:	
REASONS FOR EXCLUSION OFSTUDY FROM REVIEW ACCORDING TO PROTOCOl	
Method	No RCT / Others
Participant related	
Outcomes	
Others:	Duplication, e.t.c
TRIAL CHARACTERISTICS	
Sample size:	Study design:
No. randomized:	No excluded: Funding:
Recruitment method:	

Length of follow-up = from ---- to -----	Conflict of interest statement:
No. of drop out = Reasons for drop out:	Loss to follow up symmetric in both arms?

Study methods - Risk of bias

Adequate sequence generation Was the allocation sequence adequately generated?	Describe:	Low / High risk / Unclear
Allocation concealment Was allocation concealment adequate?	Describe:	Low / High risk / Unclear
Blinding Was knowledge of the allocated intervention adequately prevented during the study?	Participant: Dentist/ Dental technician / Dental assistant: Outcome assessor: Describe:	Low / High risk /Unclear Low/ High risk / Unclear Low / High risk /Unclear
Incomplete outcome data addressed Were complete outcome data adequately addressed?	Low/Unclear / High risk Describe any loss of participants to follow-up at each data collection point: Describe any exclusion of participants after randomisation: Was the analysis intention to treat? If not has the data been able to be re-included	
Free of selective reporting bias Are reports of study free of suggestions of selective reporting bias?	Low risk/ Unclear / High risk Describe: Need to say whether the protocol of the study was available or not and whether all pre-specified outcomes were addressed	
Free of other bias Was the study apparently free of other problems that could put it at	Low risk / Unclear /High risk If the study was stopped early, explain the reasons:	

high risk of bias? **Funding**	Describe any baseline imbalance: Describe any differential diagnosis:

Number of participants entering trial	
15% or fewer excluded	
More than 15% excluded	
Analysed as 'intention-to-treat'	
Unclear	

ADDITIONAL INFORMATIONS

Were withdrawals described? Yes No Not clear

Discuss if appropriate……

Outcomes for main analysis

Outcome Measures (Dichotomous)	**Total number of participants in study =**			
	<u>Intervention group</u> **Total no. in study** =		**<u>Control group</u>** **Total no. in study =**	
	Events	Total	Events	Total
Primary outcomes:				
Secondary outcomes:				

Outcome Measures (Continuous)	**Total number of participants in study =**					
	Intervention group Total no. in study =			**Control group** **Total no. in study =**		
	total	mean SD		total	mean	SD
Primary:						
Secondary:						

Outcomes for sub-group analyses

Outcome Measures (Dichotomous)	**Total number of participants in study =**			
	Intervention group total no. in study =		**Control group** **Total no. in study =**	
	events	Total	events	total
Primary:				
Secondary:				

Outcome Measures (Continuous)	**Unit of measurement**	**Total number of participants in study =**			
		Intervention group Total no. in study =		**Control group** Total no. in study =	
		total	mean SD	total	mean SD
Primary:					

Secondary:					

Appendix 3: Assessment of risk of bias in the included studies

(1) Random sequence generation (checking for possible selection bias)

For each of the included trials, the method used to generate the allocation sequence to facilitate an assessment of whether it should produce comparable groups was described in detail.

The method was assessed as:

- Low risk of bias (a truly random process, e.g. random number table; computer random number generator);

General conclusions

Brief summary of study authors' main findings/conclusions:

Notes:

Exclusion after data extraction:

Reasons for exclusion: (study design? participants? interventions/ outcomes? attrition? bias?)

Dates: Date data was extracted and by whom?Date checked and by whom?

- High risk of bias (a non-random process, e.g. odd or even date of birth; clinic or hospital record number);
- Unclear risk of bias (the process was deemed as such when the method used was not described clearly)

(2) Allocation concealment (checking for possible selection bias)

For each of the included trials, the method used to conceal allocation to interventions prior to assignment was described, and it was assessed whether the intervention allocation could have been foreseen prior to recruitment, during recruitment or changed after assignment.

The method was assessed as:

- Low risk of bias (e.g. telephone or central randomisation; consecutively numbered opaque sealed envelopes);
- High risk of bias (open random allocation; non-opaque or unsealed envelopes, alternation; date of birth);
- Unclear risk of bias (method of allocation not clearly or explicitly stated)

(3.1) Blinding of participants and personnel (checking for possible performance bias)

For each included trial, blinding was described in terms of the methods used to blind the study participants and personnel from the knowledge of which intervention a participant received. Studies were deemed as low risk of bias if they were blinded, or alternately, we judged that the lack of blinding would have a negligible effect on the results. Blinding was assessed separately for different outcomes.

The methods of blinding were assessed as:

- Low, high or unclear risk of bias for participants
- Low, high or unclear risk of bias for personnel

(3.2) Blinding of outcome assessment (checking for possible detection bias)

For each included trial, the methods used were described in terms of blinding of the outcome assessors from the knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes as:

- Low, high or unclear risk of bias

(4) Incomplete outcome data (ascertaining any possible attrition bias due to the amount, nature and handling of incomplete outcome data)

For each included trial, and for each outcome, the completeness of data including attrition and exclusions from the analysis was described. Attrition and exclusions if any were reported and the numbers in the analysis at each stage (as compared to the total randomised participants), reasons for attrition or exclusion were reported, and there was a balance across groups regarding missing data or were related to outcomes.

The methods to ascertain incomplete outcome data were assessed as:

- Low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- High risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; considerable deviation from the intervention received from that assigned at randomisation but reported 'as treated');
- Unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

For each included trial, selective reporting was described in terms of how we investigated the possibility of selective outcome reporting bias and what we established.

The methods to ascertain selective reporting were assessed as:

- Low risk of bias (here, all of the pre-specified outcomes of the study and all expected outcomes of the review were reported);
- High risk of bias (here, not all the pre-specified outcomes of the study were reported; one or more reported primary outcomes were not pre-specified; incomplete reporting of outcomes of interest and hence the information rendered unreliable; failure to include results of a key outcome in the study that would have otherwise been reported);
- Unclear risk of bias (no clear description or explanation was given regarding the outcomes)

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

For each included trial, any important concerns regarding other possible sources of bias were described.

Each study was assessed whether free from other problems that could put it at risk of bias as:

- Low risk of bias;
- High risk of bias;
- Unclear whether there is risk of other bias.

(7) Overall risk of bias

Judgments were pronounced as to whether studies were at high risk of bias as per the criteria in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Regarding (1) to (6) above, the magnitude and direction of the bias was assessed and whether these findings were likely to impact on the findings were contemplated.

Appendix 4:Study Protocol

Mechanical debridement combined with antibiotics in the treatment of periodontitis: effect on systemic biomarkers.
A Systematic Review.

Background

Periodontal disease is one of the most common public health concerns worldwide, constituting the main cause of tooth loss in adults, prevalent in 5-15% of most populations [1]. Chronic periodontitis is a highly prevalent inflammatory disease that affects the periodontium. Although the prevalence of the disease varies in different countries, it can be estimated that, in the USA, about 50% of the adult populationabove 30 years of age present some form of periodontitis, ranging from mild to severe[2].According to a systematic review by Kassebaum et al. (2010), severe chronic periodontitis (SP) was the 6th most prevalent non-communicable disease (NCD) in the world, affecting 10.8% of the population (Uncertainty Interval [UI]: 10.1% - 11.6%) or 743 million people across the globe [3]. In addition, prevalence of SP increased with age, revealing a steep increase between the 3rdand 4th decades of life, with a spike in incidence around the age of 38. At the age of 40, the prevalence of SP had reached its peak [3].

The etiology of periodontitis is complex and includes the presence of specific pathogens, such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia*in in a susceptible host [4].Potential risk factors that increases the odds ratio for periodontitis include tobacco use [5], diabetes [6], unhealthy diet [7], genetic factors [8], stress [9] and excessive alcohol consumption [10].Central to the disease process of periodontitis is the formation of biofilm on tooth and root surfaces, which triggers the immune system. The inflammatory host response affects the tissues surrounding the teeth, resulting in destruction of the periodontal apparatus [11]. In its advanced stage, periodontitis can lead to difficulty in mastication and speech and can adversely affect generalwell-being and quality of life [12]. The diagnosis of periodontal disease is based on clinical measures of inflammation, such as bleeding on probing, pocket probing depth and attachment loss, as well as radiological evidence of bone destruction [13].

The effects of periodontitis seem to go beyond the local oral tissues, affecting the systemic environment[14,15]. A number of studies have suggested an association between certain NCDs, socioeconomic status (SES), adverse pregnancy outcome and periodontal infection (Lalla 2011, Gomes-Fihlo 2010, Tonetti (2013)[16,17,18]. Additionally, periodontitishas been associated withcertainconditions, such as heart disease [19], diabetes [52,53,54,55], respiratory disease [20] and systemic inflammation[21,22].

Periodontal treatment entails the elimination of biofilm and microbial deposits from the root surfaces in order toreduce the inflammatory host response and tissue destruction[23,24]. Although there are several treatment approaches for periodontitis, conservative mechanical debridement (scaling and root planing [SRP]) hasbeen the most common therapy [25].Depending on theseverity of inflammation; mechanical debridement combined with systemic antibiotics has been advocated as a treatment option. There is currently insufficient scientific evidence to support or refute whether systemic antibiotics effectively enhance the results of mechanical periodontal treatment[26,27,28,29,30,31].

Description of the intervention and how the intervention might work

Previous meta-analysis [32,33,34]and systematic reviews [35,36,37] have looked at the benefits of antimicrobial agents in providing systemic clinical benefit. Systemic antibiotic therapy is effective in reaching microorganisms which are otherwise inaccessible to scaling instruments and local antibiotic therapy [38]. SRP alone (without adjunctive antibiotics) have been shown to reduce the risk for cardiovascular disease (CVD) and diabetes mellitus by improving plasma levels of inflammatory (CRP, IL-6, TNF-α) and metabolic (HbA1c) markers of endothelial function [39].

Several molecules have been identified as potential biomarkers for periodontal disease, including proteins, cytokines, receptors and enzymes. These biomarkers have been identified and measured in the gingival crevicular fluid (GCF), which provide information on the local periodontal destruction, in serum and saliva. In saliva, high levels of matrix metalloproteinase (MMPs, including MMP-8, MMP-14 and TIMP-1) have been associated with periodontitis [40]. Marcaccini et al. reported that salivary MMP-8 and MMP-9 can be used as indicators of periodontal treatment response. Systemically, serum or blood biomarkers have been associated with periodontal disease; C-Reactive protein (hs-CRP) and inflammatory cytokines in serum have been linked to periodontitis [41]. Periodontitis leads to the production of local inflammatory mediators which enter the systemic circulation, thus causing an inflammatory burden [42]. An increase in the serum C-reactive protein (CRP) levels is indicative of the inflammatory burden, as seen in periodontitis patients [43,44,45,46,47,48]. Simultaneously, bacteria and their products enter the systemic circulation causing an infectious burden [42]. Circulating oral bacteria stimulate hepatocytes to secrete CRP [49,50,51]. Increased levels of CRP associated with periodontitis results in insulin resistance and subsequent impaired control of blood glucose in type 2 diabetes mellitus (DM2) [52,53,54,55], which in turn increases the levels of HbA1c [56,57].

The most studied inflammatory biomarkers in relation to periodontitis are:

1. Matrix Metalloproteinase (MMPs)
2. Tissue Inhibitors of MMPs (TIMPS)
3. Cytokines/Interleukins (IL-1β, IL-6 & IL-8)
4. C-Reactive Protein (CRP)
5. Glycosylated Hemoglobin (HbA1c)

TNF-α is a cytokine, which has been omitted from the review, as it exhibits an early rise and fall after an inflammatory stimulus, being an unstable biomarker, with very low basal levels that escape most commercial detectionassays [58].

Matrix Metalloproteinase (MMPs)

MMPs are a group of proteolytic enzymes that play an important role in the degradation of collagen and extracellular matrix in conditions such as osteoarthritis, tumour cell invasion, rheumatoid arthritis and autoimmune skin lesions [59]. In the periodontal disease process, fibroblasts, neutrophils,

macrophages, keratinocytes and endothelial cells can produce MMPs. MMP-8 is a significant biomarker in periodontitis, also known as collagenase-2 or neutrophil collagenase.

Tissue Inhibitors of MMPs (TIMPs)

TIMPs are endogenous tissue regulators of MMP activity. A variety of cells produce TIMPs, including endothelial cells, fibroblasts, macrophages and keratinocytes [59]. In periodontitis, the TIMPs and MMPs proportion is disturbed/skewed toward higher levels of MMPs [60]. TIMPs have an inhibitory effect on MMP-8 and MMP-9, enzymes which predominantly breaks type-1 collagen in periodontitis.

Cytokines

Cytokines are a group of proteins released in response to an activating stimulus and they function through binding to specific cellular receptors [61], being produced by a variety of cells in the human body[59]. Interleukins are among the cytokines that seem to be linked to the inflammatory response seen in chronic periodontitis [62].

Interleukin-1β (IL-1β)

IL-1β is responsible for bone resorption and has an inhibitory effect on bone formation. It stimulates prostaglandin synthesis and facilitates the up-regulation of inflammatory response [63].

Patients suffering from periodontitis have increased IL-1β levels, which can be measured in the GCF as well as in the periodontal tissues. The IL-1β functions as a biomarker for periodontal destruction. Studies have found a correlation between levels of IL-1β and the severity of periodontitis [64].

Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine, which regulates the host response to tissue injury, inducing formation of CRP [65]. Together with IL-1, IL-6 facilitates tissue destruction by elevating the MMP levels [66].

IL-6 is produced by monocytes, vascular endothelial cells, osteoblasts and fibroblasts in reaction to inflammatory challenges [67]. They promote immunoglobulin production by plasma cells and are co-stimulators of T-cell activation [68]. In periodontitis, initial host response is part of the acute-phase

response initiated by the activation of fibroblasts, endothelial cells and local macrophages, which lead to the release of the TNF-α, IL-6 and IL-1β mediators [69].

Interleukin-8 (IL-8)

IL-8 is a constituent of the IL-8 supergene family. It is able to recruit and activate polymorphonuclear neutrophils (PMNs), reason why it has also been linked to inflammation [70]. Lagdive et al. (2013) have found that high levels of IL-8 in the GCF of adult patients correlated with destruction of the periodontal tissues.

C-Reactive Protein (CRP)

CRP is produced by the liver and considered as a biomarker for several conditions, such as inflammatory disorders, osteomyelitis, systemic inflammation, neoplasms, vasculitis and rheumatoid arthritis [71]. High sensitivity CRP (hsCRP) is able to estimate cardiac and transient ischaemic attack (TIA) [71]. Several studies support the finding of high levels of serum CRP in patients with periodontitis [71]. DanisiaHabaet al. (2011) proposed that the higher levels of CRP in chronic periodontitis patients could make them more susceptible to cardiovascular disease [67].

Glycated Haemoglobin (HbA1c)

Diabetes Mellitus is one of the most studied risks factors for periodontal disease. Studies have reported that poor glycaemic control is correlated with higher risk for periodontal disease [49]. It has been suggested that there is a 2-way relationship between glycaemic control and periodontal disease [72]. Improvement in glycaemic control seems to decrease the risk for periodontitis while periodontal treatment might improve glycaemic levels in type 2 diabetes mellitus patients [73]. Glycaemic control is the most important factor in the prevention of diabetes complications. Glycated haemoglobin (HbA1c) is used as an indicator of serum glucose levels during the 4-month life-cycle of the red blood cell, thus being a surrogate marker for glycaemic control [74].

Periodontal therapy without antibiotics

There are numerous studies illustrating the positive effect of SRP alone on systemic biomarkers. Good glycaemic control seems to be a pre-requisite for mechanical debridement to have a decreasing effect on HbA1c in periodontitis patients with type 2 diabetes mellitus [75,76,77,78].A number of ramdomized clinical trials (RCT) have demonstrated the efficacy of mechanical debridement in decreasing HbA1c levels in blood [79,80,81,82,83,84,85,86,87,88]. Regarding MMP-8 levels, a study

showed that salivary MMP-8 decreases after mechanical debridement [89]. As for IL-1β, four studies have confirmed the efficacy of SRP in reducing salivary IL-1β levels [89], blood/circulating IL-1β [90,91] and GCF IL-1β levels [92]. The GCF levels of TiMP-1 have also shown a decrease after mechanical debridement [93].

Amongst the RCT's evaluating IL-6 levels, four studies revealed a decrease in circulating/blood IL-6 levels [86,94,95] and GCF IL-6 levels [92] after mechanical debridement. With regardsto IL-8, three studies demonstrated a decrease in salivary IL-8 levels [89], GCF IL-8 levels [96] and circulating IL-8 levels [86]. Ten RCT studies demonstrated a decrease in blood CRP levels after mechanical debridement/SRP alone [77,82,83,94,95,97,98,99,100,101].

Periodontal therapy with antibiotics

Mechanical debridement together with doxycycline antibiotics [or sub-antimicrobial-dose doxycycline (SDD)] has been shown to decrease the HbA1c levels in blood biomarkers in type 2 diabetes mellitus [31,102,103,104,105,106,107,108,109,110,111].

Regarding TIMP-1, in one study, SDD was able to down-regulate gingival crevicular fluid (GCF) levels of EMMPRIN, which is an up-regulator of MMP's, and this was associated with increased TIMP-1 levels [112]. Reports also suggest that doxycycline associated with non-surgical periodontal treatment (NSPT) increasedGCFTIMP-1 levels [113,114]. Lower IL-6 levels have been reported in both GCF[30,114] and serum[31,115] after NSPT and antibiotic therapy. GCF MMP-8 levels have also shown a reduction in many studies on SRP combined with antibiotics [103,105,114,116,117,118].

Reduced serum CRP and IL-1βlevels have also been associated with NSPT combined with SDD [115,119,120,121,122]. Lastly, salivary IL-8 levels decreased after SRP and antibiotic therapy [123].

Various antibioticsused in the treatment of periodontitis

A wide variety of systemic antibiotics have been used in the treatment of periodontitis. The most widely used are: Amoxicillin (AM), Azithromycin (AZ), Clarithomycin (CLAR), Doxycycline (DOX), Metronidazole (MET), Moxifloxacin (MOX), Ornidazole (ORN) and Clavulanate (CLAV). AM combined with MET is the most popular combination in the treatment of periodontitis [124].

WHY IT IS IMPORTANT TO DO THIS REVIEW

Diabetes mellitus and cardiovascular diseases are among the systemic diseases that have huge economic burden worldwide. Periodontal treatment has been shown to reduce glycaemia and lower HbA1c levels in diabetic patients[76,106,107,125,126]. Meta-analyses also support a positive effect of periodontal treatment on glycaemic control [127,128].

The potential benefit of periodontal therapy on glycaemic control can have major implications on a country's economics. In their study on type1 and type2 diabetes, Brod et al. (2016) pointed out that the annual costs per person for missed work-time due to post-prandial hyperglycaemia (PPH) was Euro 394.78 in Germany (given Euro 8.48 per week; 40 work weeks), £396.83 in the UK (given £8.62 per week; 46 work weeks) and U$606.30 in the USA (given U$13.05 per week; 47 work weeks) [129].

With regards to cardiovascular diseases (CVD), periodontal therapy has been shown to reduce the risk for CVD by improving plasma levels of inflammatory, thrombotic and metabolic markers [29,39,97,99] and changing the systolic blood pressure [130]. In addition, periodontal therapy normalized haematological markers levels in CVD sufferers [101] and reduced low grade systemic inflammatory markers and lipid profile [131]. Researchers have reported that the direct costs of CVD were a cumulative U$272 Billion for the USA [132], with an annual estimate of 106 Billion Euros for the European Union [133]. A plethora of studies have declared the benefits of periodontal therapy on the reduction of CRP levels, which is directly related to cardiovascular health. These findings, if proven to be conclusive, can translate into a substantial reduction in the economic burden of diabetes and CVD.

Reasons for excluding Aggressive Periodontitis from the systematic review

Chronic periodontitis is characterized by periodontal tissue destruction which is commensurate with local factors while the progression ranges from slow to moderate. In aggressive periodontitis, there is a rapid rate of attachment loss in systemically healthy patients. The scale of tissue destruction is disproportionate to the amount of plaque and calculus [134].

(1) Genetics

Studies have shown that very few subgingival bacterial species differed between chronic and aggressive periodontitis patients [135], which has led to studies on genetic predisposition [136] and familial patterns of disease [137,138,139] as potential risk factors for aggressive periodontitis.

(2) Local Risk Factors

In aggressive periodontitis, there is a lack of relationship between local etiologic factors and the amount of periodontal destruction [137]. In contrast, in chronic periodontitis, local factors play a major role [140].

(3) Rate of Bone Loss

In aggressive periodontitis, the rate of bone loss has been described as being3-4 time higher than the rate of progression of chronic periodontitis [137,141].

To sum-up, though aggressive periodontitis and chronic periodontitis share common disease manifestations and outcomes, they are likely to represent two distinct disease categories with differences with regards to disease progression, underlying causes and risk factors.

Reasons for excluding studies evaluating local antibiotics

Several reviews on local antibiotics in the form of antimicrobial irrigants [142,143,144], chlorhexidine chips [145] and subgingival chlorhexidine gel [146] have shown ineffective results. Magnusson et al. (1998) reported little long-term efficacy of antimicrobial irrigants [142], while Cosynet al. (2006) reported limited and conflicting results [145]. Nagarakanti et al. (2015) stated that evidence was insufficient regarding potential benefits of subgingival irrigation [143]. Gjermo et al. (1993) reported that subgingival antibacterial agents have no effects on periodontitis [144]. In their review,Cosyn et al(2005)concluded that subgingival chlorhexidine gel administration was not a justified treatment [146]. In contrast, a review (Jepsen et al. 2000) showed additional pocket depth reduction and attachment gain associated with local antimicrobials [147]. Hussein et al. (2007) also reported improved clinical outcomes with the use of locally delivered antibiotics [148]. Since the majority of studies have not been able to confirm the efficacy of local antimicrobials in the treatment of periodontitis, their application has been excluded from the current review.

OBJECTIVES

To assess the effectiveness of systemic antibiotics as an adjunctive therapy to mechanical treatment in the improvement of inflammatory systemic biomarkers as compared to mechanical debridement alone in chronic periodontitis.

Methods

Criteria for considering studies for this review

Types of studies

RCT'scomparing adjunctive systemic antibiotic plus mechanical debridement with mechanical debridement alone (scaling and root planing, oral hygiene and prophylaxis).

Types of participants

The participants will be individuals diagnosed with chronic periodontal disease. Subjects diagnosed with systemic disease, such as diabetes mellitus, cardiovascular diseases, chronic obstructive pulmonary disease or chronic kidney disease (minimum 18 years and above), and chronic periodontitis will also be included

Types of interventions

All interventions that included mechanical debridement combined with adjunctive systemic antibiotics.

***Comparison*:** Mechanical debridement alone or placebo or no treatment

Types of outcome measures

Primary outcomes

The primary outcomes were changes in serum/blood levels of inflammatory biomarkers (e.g. MMPs, TIMPs, Cytokines, CRP and HbA1c)before and after mechanical periodontal treatment with and without systemic antibiotics.

Secondary outcomes

Changes in the following indices before and after mechanical periodontal treatment with and without adjunctive antibiotics: gingival index, plaque index, pocket depth and marginal recession. Microbiological outcomes and adverse events were recorded as reported in each study.

Search methods for identification of studies

Electronic database search will be combined with journal hand searching. Attempts will be made to identify unpublished and grey literature. RCTs published in English from 1980 to 2016 will be considered.

Electronic searching

The following databases were searched for relevant trials:

Cochrane Oral Health Group's Trials Register

CENTRAL – Cochrane Register of Controlled Trials (of the Cochrane Library – current issue)

MEDLINE (1966 to present), EMBASE (1982 to present)

The search strategy for MEDLINE using PubMed software formed the foundation for the basic search strategy. Cochrane sensitive search filters for identifying RCTs were used.

Hand searching

Articles published prior to 1991 will be hand searched since no indexing terms for randomized trials in MEDLINE existed [149].Allarticles in parts of journals (supplements and conference abstracts) which were not routinely indexed in databases such as MEDLINE will be searched, reference lists of the included studies will be screened for additional relevant studies. We will contact experts in the field of oral health care to identify any additional published or unpublished trials. We will not apply any date or language restrictions.

Data Collection and analysis

Selection of studies

Two review authors, will independently screened the titles and abstracts of the search output to identify and select potentially eligible studies. Applying eligibility criteria using a pre-designed eligibility form based on the inclusion criteria, duplicate studies and studies that were not relevant to the review will be excluded. Full-text articles of potentially relevant studies will be retrieved, and disagreements will be resolved through discussion by consulting a third review author. The reference lists for the included studies will be screened for additional studies.

Data Extraction and Management

Data extraction form will bedesigned for extraction of relevant information. For eligible studies, two review authors will extract data using the data extraction form.

For each outcome, we will extract the arithmetic means and standard deviations (or information to estimate the standard deviations). We will resolve discrepancies through discussion or, if required, wewillconsult the third author.Wewillcheck for accuracy and when information regarding any of the above is unclear, we will contact authors of the original reports to provide further details.

Study quality assessment

Two review authors (SM and ET) will independently and in duplicate performed a quality assessment of the included studies. All trials that met the inclusion criteria will be assessed on four major criteria: randomization method, concealment of allocation, blinding of patients and care providers, and accurate description of withdrawals and drop outs rate

Kappa statistics will be used to assess the initial agreement between the review authors. Any disagreements between the review authors will be resolved by consensus.

Quality criteria, the definition thereof will be based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions.

Assessment of Risk of Bias in included studies

Risk of bias for each study will beassessed independently by the 2 review authors (SLM and ET) using the criteria outlined in The Cochrane Handbook for Systematic Reviews of Interventions [150]. The method for allocation sequence generation, the completeness of the outcome report, selective reporting and any other source of bias that can put a study at high risk of bias will be assessed. Any disagreements will be resolved by discussion or by consulting the 3rd assessor.

Measures of Treatment Effect

The effect size will be estimated and reported as mean difference (MD), and the 95% confidence interval (CI) will be calculated. In cases of inter-study heterogeneity, Random Effects Model will be used. If the pooled effect is significant, then ***p***wasto be<0.05.

Raw data (i.e. Means, SDs and sample sizes), point estimates (in block display) and CI's (in line displays) will be presented in the form of Forest Plots.

Heterogeneity Statistic (I^2), total number of participants per group, overall average effect (Z-statistics and MD statistics) in the random effects model and percentage weight given to individual studies will be appended to the Forest Plot.

Dealing with Missing Data: Levels of attrition will be noted in the included studies. Sensitivity analysis will be used to explore the effect of including studies with high levels of missing data in the overall assessment of treatment effect.

Intention-to-treat analysis will be used, hence all participants randomized to each group in the analyses will be included and all participants will beanalyzed in the group to which they were allocated to, irrespective of them receiving the allocated intervention or not. For each outcome in each trial, the denominator will be the number of randomised minus any participants whose outcomes were missing.

Assessment of Heterogeneity

Heterogeneity will beassessed using the chi-squared-based Q-statistic method and the I^2 measurement with significance indicated by $p<0.1$.

Heterogeneity between studies will be explored, quantified and controlled by way of subgroup analysis.

Patient characteristics

- Self-reported smoking status
- Initial pocket probing depth
- Immunological disease (HIV)
- Patient adhered plaque control

Treatment characteristics

- Class of antibiotics
- Baseline and follow-up time
- Number of sessions for debridement

- Supportive follow-up care

Other sources of heterogeneity identified during the review were regarded as post-hoc analysis. Sensitivity analysis will be performed, and studies classified as high risk of bias trials will be excluded.

Publication bias

No tests were performed to detect publication bias.

Conflicts of Interest

Sudhir Munasur: None declared

Eunice Turawa: None declared

UsufChikte: None declared

Dissemination of findings: The present systematic review will be published in dental journals both local and international along with journals pertaining to NCDs

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